

Torsion of the testicle.

[Frontispiece, see page 233.]

# INTERNATIONAL CLINICS

A QUARTERLY

OF

ILLUSTRATED CLINICAL LECTURES AND  
ESPECIALLY PREPARED ORIGINAL ARTICLES

ON

TREATMENT, MEDICINE, SURGERY, NEUROLOGY, PEDIATRICS,  
OBSTETRICS, GYNÆCOLOGY, ORTHOPÆDICS,  
PATHOLOGY, DERMATOLOGY, OPHTHALMOLOGY,  
OTOLOGY, RHINOLOGY, LARYNGOLOGY,  
HYGIENE, AND OTHER TOPICS OF INTEREST  
TO STUDENTS AND PRACTITIONERS

BY LEADING MEMBERS OF THE MEDICAL PROFESSION  
THROUGHOUT THE WORLD

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NEW ORLEANS

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VOLUME IV. FORTY-FIRST SERIES, 1931

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# Third Congress of the Pan-American Medical Association Held in Mexico City, July 26-31, 1931

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## MEDICAL AND SURGICAL TRENDS AS SEEN AT THE CONGRESS

By JAMES J. WALSH, M.D.

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IN SPITE of the fact that a recent English critic of American education has suggested that he wonders what would become of discussions of various subjects in American education if the word "trends" were eliminated from the language, there seems no other word to express certain medical and surgical tendencies in current medical science than by this word. There is no simpler term for summing up the main features of the transactions of the third Pan-American Medical Congress to which contributions were made not only by men from all the various Latin-American countries but also from most of the States of the United States.

Of course it would be impossible to give any adequate idea of the contents of the many papers which were read, altogether some three hundred, from twenty-four different sections. These included every one of the ordinary medical and surgical specialties as well as some more generic departments of medical interest besides. A list of the titles of the sections in which the many papers were read is of itself sufficient to indicate the wide scope of medical interests represented.

There were papers with regard to International Medical Relations and then the more practical contributions to General Hygiene, General Medicine, General Surgery, Tropical Medicine, Pediatrics, Urology, Ophthalmology, Bromatology, Practice of Medicine, Legal Medicine, Preventive Medicine, Medical Gastro-enterology, Cancer and Tumors (for now with the advance of cancer as one of the most important factors in mortality a special section is assigned to it), Psychiatry, Chemistry, Pure and Applied, Gynecology and Obstet-

rics, Infantile Hygiene, Oto-Rhino-Laryngology, Orthopedics, Neurologic Surgery, Chemical Pharmacy, Cardiology and Hematology. Manifestly scientific medicine is developing almost too broadly to be considered with anything like adequacy at a series of sessions of any medical congress and there is more and more danger that the specialists will be thrown back upon themselves and will lose contact with the general practitioners while the general practitioners will be deprived of the stimulus that comes from intimate relations with the specialists.

#### YELLOW FEVER

For a Pan-American Medical Congress, probably the most interesting subject is that of yellow fever. Ordinarily it is presumed that this disease is a thing of the past to be remembered in history but not an actuality for our day. Magazine writers and newspaper featurists are accustomed to talk of the conquest of yellow fever and of its elimination as a scourge of the tropics but that is not the opinion of the Surgeon General of the United States Public Health Service, Dr. Hugh S. Cumming, who, as director of the Pan-American Sanitary Bureau, has a special right to an opinion on this subject. His article on "Present-Day Problems in Yellow Fever" was read by Doctor Lloyd and attracted very special attention. He began with the expression, "No doubt some believe that the disease has been almost eradicated and will soon disappear from the entire world," but he added at once, "Yellow fever is by no means near extinction. There is a vast reservoir of yellow fever in West Africa; the disease still persists in certain parts of Brazil and in 1929 reappeared in Colombia, after it had presumably been eradicated in that country."

Surgeon General Cumming emphasizes the fact that it is not only possible but extremely probable that on account of increased and more rapid means of intercommunication throughout the world, yellow fever will prove in the near future to be once more a very serious problem. He emphasized that particularly increase in travel by airplane will cause yellow fever to reappear in many former endemic centers, and he even did not hesitate to prophesy that it might thus be caused to spread to countries never before infected. Only the strictest vigilance will be able to prevent its spread.





fort will enable the world to escape the scourge which yellow fever has proved in the past. The world must not be allowed to forget, then, the havoc that yellow fever has caused in times past nor must it be allowed to forget the fact that this disease still remains for us a very potential danger capable of destroying life and commerce if not kept within bounds.

When a nation is honestly reporting its cases of yellow fever the health authorities of other nations must not allow themselves to be stampeded into enforcing unreasonable quarantine. They should discourage undue and exaggerated publicity in the daily press and while taking reasonable precautions in protecting their own people they should limit those precautions to such measures as may be necessary to keep out the disease. Commercial relations should be interfered with as little as may be consistent with safety but other nations must have the right to quarantine against those places where the disease exists. Infectible territory must be protected against infection.

#### PLASTIC SURGERY OF THE FACE

Two factors have brought plastic surgery of the face into prominence in our time. The first is the destructive injuries to facial tissue consequent upon automobile accidents especially in connection with the shattering of glass and the destruction of smaller automobiles by heavy cars that are going rapidly. The other is the intense interest in the beautification of the human face which has brought about the appearance all over the world of "beauty shops" in such numbers that they nearly occupy the places formerly taken by the saloons. Dr. Arthur Palmer of New York called attention to the fact that for several thousand years, whenever there has been special interest in plastic surgery of the face, developments have taken place corresponding to that interest. Plastic surgery can be traced before the time of Christ and during the Middle Ages a number of methods especially for the making good of the loss of a nose have been developed. In those days close contact in times of conflict and the use of swords brought about destructive wounds of the face which surgeons endeavored and often very successfully to repair. These methods can now be applied to the new injuries

the effort to secure this has met with varying and unsatisfactory results.

It is easy to understand from this that the danger from yellow fever far from being a thing of the past still confronts the medical world. Sanitarians have two problems: first, to keep yellow fever out of territory that is not now infected, and second, to exterminate the disease wherever it exists. Successfully to combat yellow fever we must first know where it is. This makes it the solemn duty of all nations faithfully to investigate every outbreak of disease no matter how insignificant it may be if it in any way resembles yellow fever. It is a nation's duty, too, when the disease is found to report the fact immediately to other nations. Negligence in this matter would be little short of criminal.

Quarantine measures which afforded ample protection in the past and constituted the full guarantee against infection may now prove to be wholly inadequate. Ports and places in many parts in the world that were formerly weeks apart by ordinary means of communication are now within a few days of each other by airplane and it is easy to understand that new quarantine measures may have to be drawn up and enforced.

Recent advances in the knowledge of yellow fever as well as overconfidence in the probability of its extermination has led some people to think that the screening of cases of yellow fever and the destruction of adult infected mosquitoes may be dispensed with with safety. Surgeon General Cumming, however, emphasizes the fact that persons have been known to live in yellow fever endemic areas for years without contracting the disease when occupying sleeping quarters adequately screened against mosquitoes. The medical world is not in a position yet to mitigate to any extent thorough quarantine measures against yellow fever without serious danger of having the disease come back once more into even thoroughly civilized countries.

The Surgeon General appeals, then, to the entire medical profession, as well as to the layman who is interested in the saving of suffering to mankind, and particularly to the business man whose commercial interests are threatened, not to permit attention to the subject of the permanent eradication of yellow fever to be lost sight of. Universal coöperation is vital to success in this great undertaking. Only thorough-going international coördination of ef-

methods to secure such absolute rest for the affected lung as would promise adequate opportunity for the healing of lesions in it. There was evidently the feeling that a good many patients who failed to respond to ordinary sanatorium treatment can be greatly helped by surgical measures of one kind or another which have been developed during the past dozen years or more.

During the course of the Congress there were a series of debates in the Chamber of Deputies with regard to the question whether tuberculosis should not, under certain circumstances, be considered a professional affection, that is, a disease consequent upon the occupation that a man follows. They are deeply interested in decreasing their death rate from tuberculosis and it is well known that certain dusty occupations are particularly likely to be followed by tuberculosis. It was decided that silicosis, that is the irritation of the lungs due to the presence of stone dust, in workers employed where stones are sawed, must be considered a professional disease, and the laws require an indemnification of the workmen when they develop tuberculosis, as they do almost inevitably. The debate also included the question whether the indemnification should be paid to illegitimate as well as legitimate children. Manifestly it was considered that so many of the workmen had illegitimate children that it was felt that the disability pension ought to be extended to them as well as to the legitimate children.

The debate also extended to the question whether tuberculosis due to anthracosis or associated with the presence of coal dust in the lungs should not also be considered a professional infirmity. There are a large number of miners in Mexico, and as death takes place in these cases very often when the men are comparatively young, it was considered that the indemnification should be divided between the wife and the legitimate or natural children and if they were dependent on their son with his parents. These debates only serve to emphasize the humanitarian views that are at present current in Mexico for in this regard the Mexican legislators are in advance of our own in most States. There was a safeguard against abuse in the law that only those who had shown the presence of dust in their lungs before their tuberculosis developed should be considered as suffering from a professional infirmity. Those who already had tuberculosis before they entered the mines or the quarries were not

considered as sufferers from their trade unless there was very definite evidence to that effect.

#### CANCER

There has come to be a definite recognition of the fact that a great many of the cases of cancer that come for treatment cannot hope for radical cure and therefore the surgeon must think of the possibility of making the patient as comfortable as possible during the more or less prolonged period until the fatal termination. The dependence on drugs for this purpose has given way to surgical measures of various kinds. For cancer of the uterus as well as of the bladder and rectum, the eradication of certain portions of the sympathetic nervous system have been found to be eminently suitable for the mitigation of pain. Fortunately the operation is not difficult and does not require very special surgical skill once the anatomic technic is understood. The development of surgical treatment of cancer along these lines is a confession of failure to secure radical relief in a great many cases but it shows how much can be done to make the closing days of the patient's life ever so much more comfortable than before. The greater the experience with cancer, the less confidence there is in bringing about radical cure, but surgery is proving a help of very gratifying import just when medicine failed to accomplish its purpose of making the patient more comfortable.

#### RAT-BITE FEVER

Some cases of rat-bite fever were reported to the Congress and as they have recently been reported from France also it is clear that the affection is commoner than has been thought and that probably its real diagnosis and significance has often been missed. In Mexico, as in the United States, there is probably a rat for every inhabitant of the country. This question was thoroughly discussed in the last (September) issue (page 235) of the *INTERNATIONAL CLINICS*, by Dr. Stanhope Bayne-Jones, who tabulated the reported cases as found in the United States, and it would seem as if the specific infective material was in the rat's mouth which causes the intermittent fever which follows the bite and which produces the lesions that are so characteristic of it. The immense loss in food-stuffs caused by the presence of so many rats and the expense attached to their spoiling of food materials has failed so far to bring about

their extermination or even their reduction in numbers, in spite of the fact that it is the rat flea that carries bubonic plague, so that the question is whether rat-bite fever and its occurrence may not arouse popular sentiment in such a way as will bring about the effective extermination of these rodents.

#### TYPHUS FEVER

There had been a limited outbreak of typhus fever in one of the suburbs of Mexico and American doctors present at the Congress had the opportunity of seeing some of the cases, particularly in children, in full eruption with the little red-cloak appearance which suggested the old name of tabardillo. Typhus fever has been well under control in Mexico in recent years but may readily occur in epidemics if proper sanitary precautions are not taken. A jail was the source of the infection in this case just as is so often true in old histories of typhus fever. The Mexicans were rather surprised to find that certain cases of this disease had occurred in New York City and had been thought to be mild typhoid fever or paratyphoid fever. Doctor Brill showed the distinction of the affection from typhoid and paratyphoid and for sometime the disease was named after him, but it was shown to be true typhus existing endemically in New York but occurring only in a very mild form. The use of the hammock for sleeping purposes in many parts of Mexico probably has saved the population from epidemics of this affection in the past because it does away with the tendency for vermin of various kinds to accumulate as occurs in beds.

#### SPINAL ANESTHESIA

A very definite impression was produced by a series of papers and by the view of the practice in some of the large hospitals of Mexico that spinal anesthesia is on the way to replace inhalation anesthesia to a great extent. Some of those, who had thousands of cases of spinal anesthesia to report, declared that they felt that it saved a great many valuable lives and above all prevented the development of various pneumonic affections which occurred as the result of the irritation of the respiratory anesthetic. The absence of vomiting and of paralytic ileus after the operation was particularly favorable for the patient. There was no tearing out of the suture wounds

by cough as sometimes happened after inhalation anesthesia and the nursing staffs were saved a great deal of postoperative solicitude. Dr. Shuler Fagan of Los Angeles, California, after an experience of 1,700 cases without shock, did not hesitate to say that while there were dramatic deaths in connection with spinal anesthesia it was on the whole a life-saving procedure. The low pressure which so often proved dangerous in spinal anesthesia could be controlled by means of ephedrine and patients usually could smile and talk during the operation without any disturbance. Even amputation at the thigh in the old could be done without shock and without complication.

#### SURGERY OF THE SYMPATHETIC

The surgery of the sympathetic attracted no little attention during the Congress. The palliative effect of sympathectomy in cases of cancer of the bladder, the uterus or the rectum, has now come to be recognized as a very valuable resource in the terminal conditions of extreme pain which so commonly develop in these cases.

The surgery of the sympathetic, however, in relation to the kidney, seems to be the most important application of it. Dr. Elmer Hess', of Erie, Pennsylvania, paper on this subject will be found on page 28 of the present number of the *INTERNATIONAL CLINICS*.

Renal sympathectomy seems to be of very great value in the cases of floating kidney in which there are gastro-intestinal symptoms especially nausea and severe stomach discomfort. The rule in these cases is to devote a year to other measures such as properly fitting corsets and pads of various kinds. If relief is afforded in this way then recourse is not had to renal sympathectomy. In obstinate cases, however, where the discomfort continues in spite of everything that can be done, then renal sympathectomy offers a resource that has proved of very great value in a series of cases. So far no contraindications to the operation have been discovered and no complications have followed. In some of these cases there proves to be a kink in the ureter because there are certain adhesions between that structure and the peritoneum where the ureter passes on its way to the bladder and stripping of the ureter so as to free it may be necessary.

The question that comes up for special consideration is the possibility of renal sympathectomy proving of value in certain forms of

nephritis. Sympathectomy encourages a freer flow of blood through the kidney, increases the amount of urine though at lower specific gravity, but adds to the capacity of the kidney to eliminate various materials from the blood which in nephritic cases may be retained in the system with serious degenerative results. The question whether this may not prove a valuable procedure in the treatment of nephritis remains to be solved.

The French investigators who first used sympathectomy suggested as did Edebohl years ago the stripping of the capsule of the kidney and its suture to the large muscle. It was thought that this might lead to the formation of a new circulation to the kidney with favorable results for its function. In Doctor Hess' hands, however, neither the stripping of the capsule nor the nephropexy seems necessary and he has succeeded in obtaining very interesting results by simple sympathectomy. His work opens up a new field in surgery that promises to be of very great service in painful conditions of various kinds which have often been the despair of the physicians. It would seem as though most of the large organs of the abdomen can be affected favorably whenever there are painful conditions associated with degenerative lesions of one kind or another in them. Doctor Hess' work has been controlled by the observation of others and has met with distinct commendation from distinguished surgeons.

Most of the mornings of the Congress were taken up with visits to the hospitals of the city of Mexico where operations were done by the members of the staffs. Perhaps the greatest surprise for American physicians from north of the Rio Grande was to find that in some of the large hospitals of Mexico they were still using old-fashioned cocaine for the production of spinal anesthesia in place of novocaine. Their experience seemed to be reasonably satisfactory and their mortality was not disturbing. Many of the Mexican surgeons believed very firmly in spinal anesthesia because in their experience it had done away with many disturbing complications and sequelae at operations and particularly had eliminated that very disturbing post-operative condition, paralytic ileus, which is such a mortality factor in modern surgery.

The operating rooms of these Mexican hospitals were exceedingly up-to-date and it is evident that patients are being given the advantage of every possible development of modern surgical technic.

Some of the visiting physicians made it a point to visit the oldest hospital on this continent, that of Jesus Nazareus, which was built originally by Cortes in 1524. The building still standing in Mexico City is not the hospital that was erected by Cortes but one that replaced it to a very great extent in the seventeenth century. It has two beautiful courtyards, in the rear of one of which there are some fresco decorations being recovered from behind the whitewash that were in the original hospital of 1524. The hospital is a very beautiful one and Miss Nutting and Miss Dock in their "History of Nursing" suggest that it is one of the most beautiful hospitals ever built on this continent.

Visitors were somewhat surprised to find that the old hospital had operating rooms that had been built in the last few years and that represented the last word in hospital operating-room equipment. It was very clear that the hospital foundation made by Cortes must have continued all down the centuries since to be an important factor in the organization of treatment for the poor of the city and particularly the Indians, for Cortes dedicated it in retribution for any sins that he was not aware of. A good many people might be inclined to think that the Conquistador had enough to answer for without going far afield to make up for offenses that he was unconscious of, but probably the character of no one has been so well vindicated as that of Cortes in recent years and this hospital foundation of his remains for over four hundred years now a monument to his good will toward the people whom he conquered.

#### ARTERIO-VEINUS-ANASTAMOSIS

Dr. Wayne Babcock of Philadelphia called attention to the unsuccessful results which accrued from the old methods of treating aneurism by means of ligatures. These used to be the star operations of surgery a hundred years ago and even less attracting a great deal of attention. The after-results, however, were far from satisfactory. Doctor Babcock has found that in a number of these cases the performance of arterio-venous-anastomosis may bring about a much more satisfactory result than any which was obtained by the old method of ligature. This procedure also seems to relieve in a number of patients conditions of tension in the circulation, especially those which are accompanied by severe pain. The application of hy-



draulic laws to operation upon the vascular system promises to introduce a new feature into surgery that may prove to be of distinct benefit in a number of cases which up to the present time have seemed to be hopeless in their prognosis and which unfortunately have only too often been associated with extreme discomfort.

#### DIABETES

The feature of the modern treatment of diabetes that was emphasized at the Congress was that now with insulin enabling the sugar problem to be solved to a great extent in favorable cases, the obesity element in diabetes must come up for special consideration. Fat in the diet of diabetics becomes almost as important as sugar and starch were before the introduction of insulin. Doctor Geyelin of New York, after a study of six hundred cases that had been under observation for a period of nine years, has found that with a low fat content in the diet less insulin is required, there is a definite reduction in the incidence of hypoglycemia and the occurrence of high sugar content in the blood is much less common. Besides there is a reduction in the arterio-sclerosis of the legs and the patients have more energy and are able to carry on various occupations with much more success. They present much better subjects for operations if operative surgical intervention is required and infections which may develop are treated with much more satisfaction than is possible under less rigid dietary restrictions with regard to fat.

#### THE DRUG ADDICT PROBLEM IN MEXICO

While all the rest of the world is occupied just now with the question of opium in its various forms and especially morphine and heroin as well as with cocaine, the Mexicans have a very special problem in the use of what is known as *la marihuana*, which is a special native form of cannabis Indica or Indian hemp, or as it is called in French, *chavre Indian*, or in Arabic, hashish. Dr. Gregory Orneto Barenque calls special attention to this because it is raising new problems in psychiatry and demands revision of the penal code. It is often said that the drug is not native to Mexico, but Doctor Barenque points out that it is described in the well known *Historia Universal de las Cosas de Nueva España* written by Father Bernardino de Sahagun nearly four hundred years ago though the

work was published only a hundred years ago by Lord Kingswell. Recently mariguana was discovered growing in Philadelphia, it evidently having been planted by some one who knew about its narcotic properties.

From very early times it has been known that this drug exercised effects upon addicts which made them to a great degree irresponsible. It may be obtained very readily in Mexico and is consumed as a rule by smoking. Cigarettes made of it can be rolled as readily as those of tobacco and there is no doubt that it produces rather serious hallucinations. In small doses mariguana like haschish or cannabis Indica is a rather powerful stimulant of the mental faculties as well as of the sensory and motor powers. There is a definite sense of well being that occurs in connection with it and if the dose is not large muscle tiredness can be overcome, but in larger doses it has exactly the opposite effect and disturbs these functions, provoking incoördination in gait and after a while causes sleep which deepens into stupor and coma.

In association with other drugs its effects are very much heightened. A man who smokes mariguana while under the influence of alcohol requires very much less of the drug to produce profound effects on him. The phenomenon of delirium in connection with mariguana is very much more likely to occur when an individual is under the influence of alcohol. The outbreak of the delirium may be very serious and it may take a group of persons to control a patient under these circumstances. If the alcohol is taken after the mariguana, however, it does not seem to add to the effect of it, no matter how large the quantity of alcohol that is taken.

The association of cocaine and mariguana is very much worse than that of alcohol and the Mexican drug. The victim becomes the subject of delirious ideas of persecution, and is capable of doing serious injury to others. They seem to be masters of almost superhuman force and destroy everything, nothing holds them and they overcome what seem to be insurmountable obstacles. If the mariguana is followed by cocaine the patient is likely to seek solitude and may have wonderful visions and even be stimulated to the making of poetry or song. Heroin and mariguana produce extreme sexual erythism in which a patient becomes capable of almost any offense in order to satisfy his passions. This is all the more important to

realize because all the psychiatrists who have devoted themselves to the study of addicts of heroin have noted the sexual frigidity which follows its use in any quantity.

The combination of mariguana and morphine produces a definite series of physical symptoms. There is precordial anguish accompanied by intense epigastric pain. Then follow the mental symptoms. There are ideas of terror, followed by dread of being inclosed and dread of death. This is likely to be followed by a crisis with loud cries and an intense desire not to be left alone. Then comes a period of immobility, followed by stupor which lasts six to seven hours, and the patient awakens with an intolerable feeling of weakness and nausea. When the patient first smokes the mariguana and then injects himself with morphine, the latter neutralizes most of the effect of the former, diminishes hunger and thirst and causes sleep to be deeper. When the patient awakens, the morphine symptoms show themselves in intense thirst, vomiting and muscular pains.

The treatment of mariguana addicts is that of victims of acute intoxication. Once mental symptoms are developed they are extremely difficult to treat and definite degenerations take place. It was suggested that special refuges were needed for these patients and that special legislation was demanded to prevent the sale of the drug except for medical purposes. Now that there seems to be definite world agreement with regard to the amount of opium and cocaine that shall be produced, it is not unlikely that some of the addicts of these drugs who cannot procure further supplies will turn to the Mexican cannabis Indica or mariguana to take their places. It is a much more dangerous drug so far as social relations are concerned than either cocaine or opium. It is perfectly possible for those who take the drug without knowing its power to commit crimes or at least infractions of social order for which they are not responsible under the circumstances. Undoubtedly the drug has added a good deal to the criminal tendencies of certain of the population. Only careful legislation properly enforced will lessen the amount of evil which is now associated with the use of the drug.

#### INTERNATIONAL MEDICAL RELATIONS

One of the most interesting papers read before the Congress was that of Dr. Charles H. Mayo of Rochester, Minn., on "The Progress

of International Medical Relations." Doctor Mayo dwelt on the fact that medicine had developed in Mexico both before and after the conquest by Cortes and that the Aztec surgeons had proved especially skilful in the making of splints with plaster and gum and feathers, and made sutures from horsehair and even practised trephining. They knew particularly how to set fractures and to restore dislocations. After the conquest when the foundation of the University of Mexico was made, there came also the foundation of the first school of medicine in America together with the establishment of the first hospitals on the continent. Doctor Mayo gave his homage to the many distinguished physicians and surgeons who had done excellent work in Mexico. He pointed out that Doctor Lobato in 1867 anticipated the doctrines of Lister with regard to the aseptic treatment of wounds and was the first to use cotton for surgical purposes. Doctor Mayo mentioned others among the Mexican physicians who had done fine work and regretted that there was not the time to dwell further on their accomplishments.

He said that there are three principal systems of medicine in the world today, the British, the Latin and the Teutonic. Each of them has special virtues, all of them have the defects of their qualities. The problem of today is to bring about an interchange of knowledge and educate men by means of travel so that we may secure a system of cosmopolitan medicine which will combine the better elements in all these countries. "We of the republic of the North are here to learn from you and we are profoundly interested in all that you can show us." Undoubtedly these intimate professional relations will bring about better understanding among the peoples of the various countries. That word understanding is precious. The man we don't like is the man we don't know, and for all these people of different countries personal knowledge means more for understanding than anything else. Doctor Mayo invited his colleagues south of the Rio Grande to be present at some of the meetings of our medical and surgical congresses in the United States and above all he invited them to Rochester, where, he was proud to say, that there existed a chapter of the Pan-American Medical Association of which his brother is at the present time president.

After Dr. Charles H. Mayo of Rochester, Minn., had paid tribute to some of the Mexican physicians and surgeons whose cleverness in

the practice of their profession left memories of them that are not likely to fade, Dr. James J. Walsh of New York read a paper on the oldest medical book published on the American continent. This is a work consisting of four monographs by Dr. Francisco Bravo, a graduate of the University of Seville, who was practising in Mexico City in the latter half of the sixteenth century. The date of this first medical book was 1570. The first medical book published in what is now the United States did not come until more than two centuries later in 1776. There had been some pamphlets before that, but none of any particular importance. Doctor Bravo's work was an octavo of over six hundred pages containing some material that represented a real discussion of medical and surgical issues. The most interesting of his monographs is that on sarsaparilla. Doctor Bravo insisted that sarsaparilla was of no value in fever though it had been used very much and highly recommended. His study brought about the gradual elimination of sarsaparilla, that is the decoction of smilax used in that way, but it came into use again in the nineteenth century and several large fortunes were made by advertising it widely though it is now recognized to be quite useless as a medicament. The only copy of Doctor Bravo's book available for students is in the New York Public Library. There is a copy of it in Mexico but not in Mexico City and there is a copy somewhere in Spain that has been lost sight of. These facts made the references to the book all the more interesting for those from north and south of the Rio Grande.

## DUODENAL DIVERTICULOSIS\*

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THE following case seems worthy of record and is offered as an introduction to the subject of duodenal diverticulosis:

*E. V., female, widowed, aged 43:*

Previous history.—Eighteen months ago was said to have heart disease.

Present illness.—For several years has noted digestive discomfort at intervals, usually accompanied with moderate pain in upper right quadrant of abdomen.

Two months ago the pain became severe but was referred chiefly to the lower right quadrant. Between the painful attacks there was a constant dull, heavy sensation in the right side of the abdomen, chiefly above the level of the navel.

Three weeks ago she had an attack of frequency, urgency, and painful urination. This continued for two days and was followed with pain in the upper right quadrant, associated with vomiting of food and bile, and diarrhea. Is nervous and usually constipated. Has lost thirty pounds in past year.

Physical examination.—Poorly nourished, skin dry and sallow. Heart and lungs are negative; pulse is regular and slow; radial artery palpable; blood-pressure, systolic 155, diastolic 80.

Abdomen is relaxed; stomach extends from seventh rib to two inches below the navel. The caecum is dilated; moderate resistance to pressure by upper right rectus muscle; tenderness to pressure on a line midway between the navel and the tip of the ninth right rib.

*Blood examination.*—Hemoglobin, 72; erythrocytes, 3,900,000; color index, 0.9; leukocytes, 9,600; polymorphonuclears, 84; small lymphocytes, 14; basophiles, 2.

*Chemistry.*—Urea nitrogen, 28; uric acid, 3; creatinin, 2; sugar, 116.

*Test meal.*—(Ewald and Boas.) Mucus moderate in amount, starch digestion impaired, free HCl 50, total acidity 90, acetic acid present.

*Fasting test.*—Quantity aspirated, thirty cubic centimeters; color, green (bile); free HCl 44; mucus, moderate in amount.

*X-ray examination by Doctor Quimby:*

"The fourth portion of the duodenum is retracted to the right. Between the ascending and descending arms of the duodeno-jejunal angle there is a small diverticulum. A second large diverticulum occurs just above and slightly to the right of the terminal portion of the duodenum. This also lies in close apposition to the pyloric end of the stomach and first and second portions of the duodenum."

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\* Read before the third meeting of the Pan-American Medical Association, Mexico City, July, 1931.

Personal observation showed retention of barium in both diverticula after forty-eight hours. Tenderness was elicited by pressure at these points under fluoroscopic observation.

*Operation, October 29, 1930:*

*Pathology.*—The stomach was normal; the first and second portions of the duodenum were normal; the third portion ascended posterior to the second portion and crossed the abdomen posterior to the pancreas. In the third portion were two diverticula originating from the anterior internal surface and extending retroperitoneally to the right and downward.

The proximal pouch was finger-shaped, about two inches in length and contracted at its neck. The distal pouch was shorter, oval in shape and contracted to a narrow neck.

*Procedure.*—Upper right rectus incision. The second portion of the duodenum was mobilized by Kocher's method and retracted mesially. The third portion was mobilized. The neck of the distal sac was ligated, the sac excised and stump inverted. The neck of the proximal sac was clamped in an antero-posterior direction, the sac excised, and the stump sutured transversely to the long axis of the duodenum. The appendix was removed. The opening in posterior peritoneum was sutured except for a small opening through which a drain was inserted. The abdomen was closed in the usual manner.

*Pathologic report by Doctor Price.*—The specimens consist of two portions of saclike tissue lined with an intestinal type of mucosa. One sac will dilate to a diameter of one and one-half to two centimeters. The other sac is about four centimeters in length and two and one-half centimeters in width with an opening approximately in the middle of the transverse diameter. When stretched, this forms a sac about five centimeters in length and three centimeters in diameter. Microscopic examinations of tissue from the diverticulum show marked congestion and some hemorrhage which may be traumatic in origin.

No pancreatic tissue is found in the material sectioned. Some areas present a well-marked inflammatory response in which there are a large number of eosinophiles and a diffuse scattering of lymphocytes of a pathologic distribution. The muscular layer is lacking and Brunner's glands are not observed.

*Diagnosis.*—Diverticula of the duodenum showing chronic inflammation. Recovery was uneventful and symptoms are completely relieved. Patient is gaining weight and strength.

Diverticula occur in the digestive tract in the following order of frequency: colon, jejunum-ileum, esophagus, pharynx, duodenum, and stomach.

Priority in the description of duodenal diverticula has been erroneously credited to Morgagni (1761) and Sommering (1794). The first case was described by Chomel in 1710. The pouch was apparently secondary to a cholecystoduodenal fistula, for it contained "twenty-two stones of a yellow color with smooth polished surfaces." It was first recognized roentgenologically in 1912 and attacked surgically by Bauer, who performed a gastro-enterostomy to relieve

obstruction caused by pressure. Excision was first carried out by Foersel and Key in 1914.

The radiologic work has been chiefly developed by Case, Cole, Willys, Andrews and Spriggs.

The incidence of duodenal diverticula varies in the published reports ranging from 15.5 per cent. (Schuppel) to 1 per cent. (Spriggs).

In 11,664 autopsy and X-ray records, it was 1.6 per cent.

*Etiology—sex.*—Apparently the sex liability is not important. In X-ray diagnoses made by Case, 60 per cent. occurred in females. Baldwin, however, found a preponderance in men.

In 140 collected cases, which form the basis of this study, the figures were: male, 58; female, 55; not stated, 27.

*Age.*—Diverticula have been observed in young children (Sicher, Simmonds) but the majority are found in individuals past forty years of age. (In the present series the following ages are noted):

<i>Age Incidence</i>	
17 years of age.....	1
20 to 30 years of age.....	8
30 to 40 years of age.....	12
40 to 50 years of age.....	20
50 to 60 years of age.....	27
60 to 70 years of age.....	23
70 to 80 years of age.....	10
80 to 90 years of age.....	4
Old .....	2
Not stated .....	33
<b>TOTAL .....</b>	<b>140</b>

Both congenital and acquired diverticula are recognized.

*Congenital type.*—That diverticula may be congenital is suggested by their normal formation during the development of the liver and pancreas, the association of abnormal pouches with other anomalies, such as esophageal and bladder pouches and strictures of the digestive tract and the presence in some of them of all the coats of the normal duodenum. It is proved by the demonstration of duodenal diverticula in the human embryo. (Lewis and Thyng.)

The presence of pancreatic tissue in the walls of some pouches has been offered as additional evidence but is also credited with weakening the muscle layer and favoring the formation of pouches



by pressure. It has been claimed that in 60 per cent. of individuals there is a hollowing of the duodenal wall at the papilla with the orifice of the common bile and main pancreatic ducts located in the depression (Baldwin).

This has been attributed to persistence of the original diverticulum from which the liver and ventral anlage of the pancreas develop, but may as readily be explained by traction of the ducts upon the duodenal wall, particularly when prolapse of the latter is not accompanied with descent of the ducts.

*Acquired type.*—Some investigators maintain that all diverticula are congenital and explain their recognition late in life by the fact that they may persist without symptoms until they attain considerable size or until complications develop.

There is, however, evidence to suggest that many diverticula are acquired, due to pressure or traction upon a wall weakened by anatomic peculiarities or pathologic processes.

The fact that these pouches are frequently in close relation to the sheaths of large vessels or of the bile and pancreatic ducts, the absence of a muscular coat, their occurrence in individuals who are cachectic or past middle life and without changes in the liver or pancreas, is suggestive.

Diverticula have been produced artificially by ligating segments of bowel and over distending with water.

After reaching the limit of resistance, a hernia forms in the mesenteric border, where the blood-vessels penetrate the external surface of the bowel, before rupture occurs, providing the experiment is conducted with senile intestines—with children it fails.

Hauseman, who conducted these experiments in the study of a male adult whose intestinal tract showed over four hundred pouches, found that they were located along the line of the mesentery, corresponding to points of penetration of large veins. The veins, draining the intestines, pierce the inner muscular layer and extend obliquely between the two coats before penetrating the outer longitudinal layer.

Klebs first called attention to the relation between blood-vessels and diverticula. In the cases studied they were located at the points of penetration of the mesenteric vessels. He attributed this formation to traction of the intestine upon the mesentery converting the

funnel-like attachment of the intestinal wall to the entering vessels into a true pouch.

Other observers (Good, Hanau, Hauseman) have noted the same relation but attribute their formation to pressure from the intestinal contents.

In the duodenum a special factor in weakening the wall is the penetration of the bile and pancreatic ducts, which causes a greater separation of muscle fibers than do the venous sheaths and probably explains the preponderance of diverticula at this point. The duodenum is, moreover, subjected to sudden increase in tension by closure of the pylorus and sudden propulsion of gastric contents against its wall.

Among the predisposing causes have been mentioned senility, cachexia, relaxation of venous sheaths associated with circulatory stasis, atrophy of the pancreas, ptosis of the duodenum, and weakening of the muscularis by fatty infiltration or degeneration or by the presence of aberrant pancreatic tissue.

Perry and Shaw distinguish two types of acquired pouches. One is caused by traction of adhesions connecting the duodenum with the kidney, liver, colon or other structures; the wall of the intestine surrounding the pouch is normal or shows changes due to mechanical distension.

In the other, the starting point is an ulcer, the base of which yields to pressure. The ulcer weakens the muscle layer and in an early stage there may be pouching on both sides of the scar but in a more advanced stage this is transformed into a single pouch with an ulcer at the fundus.

*Pathology.*—A true diverticulum is composed of all the coats of the intestine. A false diverticulum is a hernia of the mucosa and sub-mucosa through the muscularis and is covered with serosa. Congenital diverticula are true; acquired diverticula may be true or false.

In the present series there are twenty-three true, thirty-five false, and one in which there were both true and false diverticula. In eighty-one cases no information was obtained.

The mucosa of true diverticula usually contains crypts of Lieberkühn and Brunner's glands which are lacking in the false variety. Islands of pancreatic tissue and ulcer or ulcer scars may occupy the

fundus of a sac. Chronic inflammation is frequent but acute inflammation, suppuration, and gangrene are unusual.

Many pouches are empty and show no pathologic changes, probably because of the fluidity of the contents and a wide opening into the bowel. Those with a contracted opening or in a dependent position may retain their contents many hours and lead to inflammatory changes.

Hemorrhage, gastric retention, dilated stomach, bile-tract lesions, and pancreatitis have been noted.

They occur singly in 80 per cent. of cases but as many as five have been described. The details in this series are as follows:

<i>Number of Diverticula</i>	
One diverticulum .....	114 (81.4%)
Two diverticula .....	18
Three diverticula .....	1
Four diverticula .....	3
Five diverticula .....	1
Several diverticula .....	1
Not stated .....	2
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TOTAL .....	140

They are most frequently observed in the second portion ranging from 56 per cent. in the present series to 64 per cent. in the combined statistics of Spriggs, Baldwin, Buschi, and Case.

<i>Portion of Duodenum Involved</i>		<i>Per cent.</i>
First portion .....	21	17
Second portion .....	69	56.1
Third portion .....	17	13.8
Fourth portion .....	4	3.25
Superior angle .....	3	2.4
Inferior angle .....	2	1.6
Duodenojejunal angle .....	4	3.25
Second portion and inferior angle.....	1	.8
Second and third portions.....	1	.8
Second and fourth portions.....	1	.8
<hr/>		123
Not stated .....		15
No data .....		2
<hr/>		
TOTAL .....		140

*The portion of the wall involved.*—In the first segment the majority are found in the fissural ulcer area, *i.e.*, on the anterior or superior surfaces; in the second portion, on the internal surface; and in the third portion on the superior surface.

*Diverticula in the First Portion*

Anterior surface .....	3	
Posterior surface .....	1	
Superior surface .....	2	
Inferior surface .....	1	
External surface .....	1	
Posterior and anterior surface.....	1	
Posterior and superior surface.....	1	
Not stated .....	11	
	—	21

*In the Second Portion*

Internal surface .....	55	
External surface .....	1	
Posterior surface .....	2	
Internal and anterior surface.....	2	
Not stated .....	9	
	—	69

*In the Third Portion*

Superior surface .....	7	
Posterior surface .....	1	
Not stated .....	9	
	—	17

*In the Fourth Portion*

Posterior surface .....	1	
Inferior surface .....	1	
Internal surface .....	1	
Not stated .....	1	
	—	4

*In the Second and Third Portions*

Not located .....	1	
	—	1

*In the Second and Fourth Portions*

Not located .....	1	
	—	1

*Second Portion and Inferior Angle*

Not located .....	1	
	—	1

*Superior Angle*

Internal surface .....	1	
Posterior surface .....	1	
Not stated .....	1	
	—	3

*Inferior Angle*

Inferior surface .....	1	
Not stated .....	1	
	—	2

*Duodenojejunal Angle*

Superior surface .....	1	
Not stated .....	3	
	—	4
No information .....	17	

TOTAL ..... 140

Of eighty-five cases in which the location of the diverticulum was definitely determined, sixty-four followed the concavity of the duodenum. Fifty-five of these were in the second portion; twenty-eight of them in close relation to the ampulla of Vater. It is evident, therefore, that the majority follow the concavity of the duodenum and are retroperitoneal.

The relation to the pancreas was recorded in forty-three cases:

Penetrating the head of the pancreas.....	23
Extending behind the head of the pancreas.....	14
Extending in front of the head of the pancreas.....	2
Extending towards head of the pancreas.....	4

This close relation to the pancreas probably accounts for the frequent failure to demonstrate pouches at operation, even after an X-ray diagnosis has been made, and explains the necessity for free mobilization of the duodenum when they are not readily located.

*Symptoms.*—There is no characteristic symptomatology, but when retention in the sac occurs, digestive discomfort follows.

Acute diverticulitis resembles acute appendicitis, except for the location of the lesion, causing nausea, vomiting, pain, tenderness, muscular rigidity, fever, and leukocytosis.

In chronic diverticulitis, symptoms may be due to distension and inflammation in the sac or to associated lesions; ulcer, cholecystitis, pancreatitis, duodenitis; or to changes resulting from the pressure of the sac; pyloric, duodenal or bile-tract obstruction or pressure upon

the ureter. In the majority of cases reported only the pathologic findings are described. There are, however, a sufficient number of detailed reports to establish the following symptomatology.

Attacks are usually intermittent and definitely related to taking food, occurring from one to three hours after meals. There is apt to be headache, heart-burn, flatulence, distension, acid regurgitation, nausea, vomiting, loss of weight, bilious attacks, neuritis, constipation (possibly alternating with diarrhea), occasionally jaundice, chills and fever, and urinary-tract symptoms.

Pain is frequent, either dull or sharp and burning in character, but usually gradual in onset.

It is referred to the right upper quadrant, midline, or tip of ensiform, and may radiate to the right shoulder, scapula, or lower dorsal region. It is recorded as beginning one, two, three or four hours after meals and is sometimes relieved by food or alkalies and by lying flat on the abdomen.

Symptoms suggestive of biliary colic are explained by the frequent development of these diverticula in close proximity to the bile-ducts.

*Physical signs.*—These consist of evidences of dilated stomach, gastric retention, tenderness at Mayo-Robson's point, the umbilicus, and possibly rigidity of upper right rectus muscle. Pressure may cause pain in the back, at the end of the twelfth rib, or in the costo-vertebral angle.

*Diagnosis.*—The X-ray offers the only means of diagnosis prior to opening the abdomen. "When a duodenal diverticulum is demonstrated by X-ray, retention of barium is marked and the pouch is tender to pressure, the diagnosis of diverticulitis is justified" (Case).

*Treatment.*—Pouches that cause no symptoms should not be disturbed. Those that require treatment must be attacked surgically. The procedure will vary according to the size and location of the pouch. A small diverticulum on the peritonealized surface with a wide opening may be invaginated and sutured. The result has been satisfactory in selected cases but it seems possible for it to lead to the formation of a cyst or to cause obstruction.

A large pouch, or one with a narrow neck, should be excised and sutured transversely to the long axis of the duodenum so as not to narrow the lumen. It is desirable to reinforce the suture line with

omentum. A diverticulum, close to the pylorus, may be treated by pylorotomy or pyloric exclusion and gastro-enterostomy. A pouch in the usual position, in the third portion, imbedded in, or posterior to the pancreas, will require mobilization of the duodenum to make it accessible. Usually Koehrer's method of exposure is adequate.

Pouches at the inferior angle, or distal to it, may be exposed by the method of Vautrin and Fourche or may be approached through the posterior peritoneum beneath the transverse mesocolon. A large opening in the peritoneum and free mobilization of the duodenum will expose the posterior surface of the third and fourth portions. Drainage is indicated when the operation is extensive.

The possibility of the formation of a fistula after opening the retroperitoneal portion of the duodenum must not be overlooked and if there is doubt of the adequacy of repair, it is well to minimize the strain by duodenojejunostomy or by pyloric exclusion and gastro-enterostomy.

#### SUMMARY

Duodenal diverticula are most numerous after forty years of age, but have been observed at all ages.

They may be congenital or acquired.

Congenital diverticula are true. Acquired diverticula may be true or false. A true diverticulum contains all the coats of the intestine. A false diverticulum is a hernia of the mucosa and submucosa through the muscularis. They are usually single and are most frequently found in the second portion and usually originate on the concave surface in the vicinity of the ampulla of Vater and are apt to be in close relation to the pancreas.

The symptoms are suggestive of ulcer or gall-bladder lesions or are due to interference with gastric function.

Treatment, when required, is surgical.

## RENAL SYMPATHECTOMY\*

By ELMER HESS, M.D., F.A.C.S.

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It is with a feeling of appreciation that I find myself on the program of the Third Pan-American Congress of Medicine. It is, too, with a deep and sincere feeling that the medical men of the Americas may engender a spirit that may be father to a more definite understanding and appreciation of the virtues of the peoples who come from these countries of the Americas.

Medical men, regardless of their language, find a common ground upon which they meet. Their one purpose in life is the amelioration of human suffering. Here, regardless of color, language, or creed, we may gather to help make life, wherever we may live, more comfortable and more worth while, and as we meet and understand each other, unselfishly give ourselves for the advancement of the human race. It is my desire and yours, too, I think, that our political representatives may take the same unselfish attitude toward the illness and disease of the body politic. For only as we know and understand each other, may we return to our respective countries with a more kindly feeling and a better appreciation of the other man's problems.

My main desire in appearing upon your program, or shall I say upon our program, is, in a very humble way, to be an Ambassador of good will, not only between the United States and Mexico, but between the United States and every other country represented here today, and I hope the presentation of my results with this so-called new operation may be one method of expressing that feeling.

Renal sympathectomy is an operation that was first attempted by Papin and Ambard in Paris about 1921. Papin did it for renal pain, renalgia. D. N. Eisendrath translated the original paper and

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\* From the Urological Departments of St. Vincent's and Hamot Hospitals, Erie, Pennsylvania. Read before the Third Pan-American Medical Congress, Mexico City, Mexico, on July 27, 1931.



made the statement that Papin not only did renal sympathectomy but that, in all cases, he also did a decapsulation and nephropexy.<sup>1</sup>

Two years ago in New York, Papin gave an address on conservative renal surgery. In this address he emphasized his operation of renal sympathectomy and again stated and demonstrated that his operation was always accompanied by decapsulation and nephropexy.<sup>2</sup> At that time I took issue with him on one point. If he always did decapsulation and nephropexy it was impossible for him to give credit to the sympathectomy for the beneficial results obtained. At that time I had had some experience with the operation and felt that the ground I took was correct. I have no reason to change my opinion. Papin is given credit for being the first medical man to sever the nerve supply to the kidney for therapeutic purposes. It is believed, however, that you can be shown that the operation for which priority is claimed will do every bit as much as will Papin's operation, including as it does, the two other procedures, decapsulation and nephropexy.

My first interest in sympathectomy occurred in 1926 when I had a patient in the hospital because of a very painful kidney with practically negative renal findings, although calculus was considered. The monograph of Milliken and Karr<sup>3</sup> had just been published in the *American Journal of Urology*, the reading of which gave me my inspiration, and on March 13, 1926, my first renal sympathectomy was performed. The results were so gratifying that I have since used the procedure twenty-three times.

Fearing to become a faddist, it has been necessary to be extremely careful in the selection of all cases for the operation. An attempt has been made to cure the various patients upon whom I desired to do the operation by every other possible method of treatment. Many cases have responded sufficiently to these other forms of urologic therapy that sympathectomy was unnecessary.

I have learned many lessons from my experience with this operation and some things have been discovered which may seem obvious to you but which, to me, were new and enlightening. Since my original work, other men have been doing the operation by the technic which I shall show you, and their reports have proved that there is a place in our armamentarium for this procedure. In a

rather large group of cases a conservative procedure such as this is clearly indicated and may bring considerable relief to many patients and at the same time conserve the renal structure for future pathologic storms.

As the result of the experimental work of Milliken and Karr<sup>3</sup> the following is listed as their indications for the operation.

1. Reflex anuria.
2. Nephralgia with small non-mechanical hydronephrosis.
3. Early tuberculosis of the kidney.
4. The prevention of the reformation of renal calculi following a nephrolithotomy.
5. Certain types of nephritis.

In a symposium on renal sympathectomy before the 1929 session of the Pennsylvania State Medical Society, Milliken<sup>4</sup> added a sixth theoretical indication, namely, grave hypertension. It is Doctor Milliken's theory and I will quote his statement. "I wish to propose a theoretical indication for renal sympathectomy which may seem premature, since nothing has been done in the way of direct experimentation to support it, but which I have reason to believe will be the most valuable of all for the conservation of human life.

"It has been estimated that all the blood in the body flows through the kidneys every five minutes. If, by renal sympathectomy, we can cause all the blood to flow through the kidneys in less than the usual or normal time, it seems obvious that we would thereby relieve the systemic circulation by whatever extra amount of blood we could short-circuit through the renal system. That this would be of almost instant relief in threatening arterial hypertension can hardly be questioned. Since all these cases have a nephritic complication, the toxicity incident to nephritis would be, in a measure, relieved by the operation, if our hypothesis is correct, and strain on the cerebral vessels would be lessened at the same time.

"This aspect of the subject had not occurred to me when Doctor Karr and I were experimenting on dogs and there has been no opportunity since to corroborate the idea by taking the blood-pressure of animals before and after denervation of both kidneys, but there were certain features of the results which can be interpreted only by the assumption that blood-pressure was lowered in all such cases.

This theory, which may easily, and will, be tested experimentally, is offered at the present time with the hope that it may appear sufficiently reasonable and feasible for some bold surgeon to attempt in cases of grave hypertension when all other measures have failed. Spinal anesthesia, which lowers blood-pressure, would probably be the one of choice for such an operation."

I wish to add a seventh indication, namely, as a substitute for nephropexy.

The theoretical indications will be discussed briefly, supplying my own experiences or the experiences of others with these conditions.

#### REFLEX ANURIA

No personal experience has been had with the operation used in reflex anurias, but following my original work, other men have become interested. In a personal communication from Doctor Braasch of the Mayo Clinic, Rochester, Minnesota, on February 26, 1930, he remarks:

"My interest in this subject was aroused not alone by various articles, including your own, but also by recent experiences with sympathectomy in various other portions of the body by Rowntree, Adson, Brown, et al. of the Mayo Clinic. Recently Rowntree has been interested in the use of sympathectomy for nephritis. Several patients in whom it was done seemed to improve to a remarkable degree, particularly in cases of anuria. It seems to me this field is a most interesting one and offers a great deal in the way of future development."

Again, on March 17, 1930, Braasch writes: "The possibilities of the operation have very apparently not been determined and it gives promise of being a large factor in future renal surgery. We are particularly interested in it in connection with the treatment of that form of nephritis accompanied by anuria."

Doctor Rowntree is now preparing a paper on the subject of the renal nerves in relation to renal disease and I hope very shortly to be able to read this contribution.

#### NEPHRALGIA WITH SMALL NON-MECHANICAL HYDRONEPHROSIS

There is no question that there is such a thing as nephralgia. As to the so-called diagnosis of a small non-mechanical hydronephrosis,

I have some doubt. The technic of the individual cystoscopist would have a great deal to do with making such a diagnosis. Even the time of taking the picture might have something to do with it; that it occurs, is reasonably true, but the interpretation of pyelograms, in the vast majority of cases, is such an individual, personal thing, that I would rather not consider this diagnosis. Due to overdistention of the renal pelvis by the pyelographic medium this diagnosis might be made one day and the pyelogram made next day might be so normal that they would hardly be considered the same renal pelvis.<sup>5</sup> Nephralgia, however, or painful kidney, is a very different thing. I have been misled very often by this condition and have diagnosed calculus where none existed. If we remember that approximately twenty per cent. of kidney stones throw no X-ray shadow, it can be easily understood why such an error occurs. Nephralgia is not an objective symptom; it is purely subjective and the diagnosis must be made purely by exclusion. There are so many things that cause pain in the region of the kidney that pain, to be identified as renal, must meet certain requirements. Intercostal neuralgia, neuritis, spinal caries, various foci of infection with their accompanying symptoms, these and many other conditions must be eliminated. Then it is also reasonable to believe that renal pain, of the character from which the patient suffers, may be duplicated often by overdistention of the renal pelvis.

As a result of the intimate connection of the sympathetic system of the kidney and the viscera of the upper abdomen, all sorts of gastro-intestinal pathology may be simulated, and the gastro-intestinal tract must be eliminated as a possible cause. When the pain finally is identified as renal and the cystoscopic and pyelographic data show an essentially normal kidney, then it can be reasonably supposed that all other therapeutic measures will be unavailing. It has been my experience that cutting the nerve supply to that kidney will bring relief in the majority of cases.<sup>6</sup>

#### EARLY TUBERCULOSIS OF THE KIDNEY

I have had no personal experience with the operation in this disease. There are two thoughts, however, which I would emphasize and bring to your attention. Milliken<sup>3</sup> feels that early tuberculosis of the kidney, if we are fortunate enough to make such a diagnosis,

may be helped if not cured (theoretically), by cutting the nerve supply to the infected kidney. He offers for his reasoning the fact that it has been definitely proved that after sympathectomy, the blood supply to the kidney is greatly increased for a considerable period of time and should have a beneficial influence upon the early tuberculosis. Spitzer,<sup>7</sup> of Denver, on the other hand, who has become interested in sympathectomy from an experimental point of view, particularly in tuberculosis, took the attitude that the good kidney in early tuberculosis should be sympathectomized, thereby increasing its work, lessening the work of the tuberculous kidney and improving the disease by the rest thus enjoyed.

I do not believe that as yet Spitzer has published any of his work and in a recent chat with him I felt rather inclined to believe that he felt sympathectomy was of no real value in renal tuberculosis. He has discovered one thing in his work, however, which we can verify and that is that after unilateral sympathectomy there is a mechanical, automatic readjustment of the amount of work done by the operated and unoperated kidney, and that after several months it was impossible to tell from the functional tests which kidney had been denervated.<sup>8</sup>

#### THE PREVENTION OF THE REFORMATION OF RENAL CALCULI FOLLOWING A NEPHROLITHOTOMY

Whenever possible, kidneys have been deliberately denervated after the removal of calculi from the renal pelvis. It is not known whether this operation will have a tendency to help prevent the reformation of renal calculi, but so far none of the series have experienced another attack of renal calculus.<sup>9</sup> In removing a calculus from the ureter a sympathectomy is never done because it is believed that the added trauma of delivering the kidney is unjustifiable from the standpoint of possible results as a preventative procedure. The theory is that a more dilute urine of lower specific gravity will be eliminated from the sympathectomized kidney and therefore reformation of calculi will be less likely.<sup>3</sup>

#### CERTAIN TYPES OF NEPHRITIS

The future of sympathectomy in the treatment of certain types of nephritis with anuria or hypertension, or in those cases in which

we, for want of a better name, call essential hematurias, is a question for the future to solve. I have had no experience with it in these conditions. The experiences of Rowntree and Braasch have been cited, as well as Milliken's ideas on renal sympathectomy in hypertension. In the therapy of this group of cases there is enormous room for improvement.

This large group of cases is presented to you for careful study and investigation. As the opportunity presents, I intend to try it with these indications. It has been definitely proven by the large number of cases in the series that the operation does not injure in any way the functional ability of the kidney, nor does it leave the kidney crippled. In these nephritics, bilateral denervation will be necessary. Bilateral denervation has been done in one case and the operation is practicable and in no way seems to be detrimental.<sup>5</sup>

There is opportunity here for an enormous amount of original experimental work. Who knows but that some of us, ten years hence, may find that certain types of nephritis, which today are incurable and unhelpable, may be benefited by this very simple procedure.

Your attention is again called to Milliken's sixth theoretical indication. The subject is left in your hands.

#### AS A SUBSTITUTE FOR NEPHROPEXY

Earlier in the paper I told you that I took issue with Papin on decapsulation and nephropexy. Mr. Frank Kidd of London, England, spoke very highly of nephropexy in certain types of cases before the American Urological Association this past year.<sup>9</sup> There are, doubtless, many urologists and many general surgeons who consider that a ptotic kidney with or without symptoms is sufficient indication for this operation.

Braasch of the Mayo Clinic, Lowsley, Kirwin, Young, Deming, and others feel that nephropexy in the vast majority of these cases is not the proper surgical procedure. Most of the men who do the operation hook the kidney to the twelfth rib. In my opinion, this disturbs the normal physiology. If you will take the trouble to take two pyelograms, one in inspiration and one at expiration, you will find that the normal kidney has a considerable normal excursion. Just because a man or a woman has an easily palpable

kidney is no reason why that organ should be the cause of a vast nervous symptom complex. It has been proved to my own satisfaction that a movable kidney will not cause any great variety of symptoms unless there is an accompanying kink of the ureter with dilatation of the renal pelvis, and the vast majority of these organs, ordinarily, do not give symptoms. It is also believed that the symptoms that they do cause are primarily the result of obstruction to the ureter plus stasis of the urine in the kidney pelvis, plus infection. A chronically infected or distended kidney is naturally going to be a sensitive one.

If you will recall for a moment your anatomy, you will remember that the ureter is rather firmly bound to the parietal peritoneum up to a point approximately four or five centimeters from where it enters the renal pelvis. If the renal pelvis descends below this point there is very apt to be angulation and stagnation. This, naturally, is going to cause symptoms. Or if there is obstruction lower down from any cause, the misplaced kidney would be more apt to suffer from the effects of stasis and superadded infection.

The controversy as to whether to suspend these kidneys has waged pro and con for years. Many of these conditions can be cured by catheter drainage and the wearing of a proper corset or belt. To my mind, nephropexy as now performed by the majority of leading urologic and general surgeons, is a non-physiologic procedure, therefore an undesirable one. In inspiration the kidney normally descends anywhere from one-half to three inches. The ribs flare outward and if the kidney be hooked to the ribs, it cannot descend in inspiration but is pulled further up and further out by its anchor. Mechanically and physiologically, this seems bad.

It has been found in some of my cases that it does not really matter where the kidney is placed just so long as there is no obstruction and no stasis in its pelvis. If an operation could be devised that would reasonably fix the kidney in some fairly constant given position; if the ureter could be unkinked as it were, and if drainage could be assured, these misplaced kidneys would cause little, if any, trouble. You are referred to the many cases of renal dystopia that give no symptoms through a long life and are only discovered by chance at autopsy.

The first case where this was noticed occurred in a school teacher, a nun, who had a renal sympathectomy for a right kidney that was giving disabling, painful symptoms periodically. Upon preoperative study this kidney was found only to give symptoms when it descended below the crest of the ileum. It was concluded that due to the fixation of the ureter to the parietal peritoneum, there occurred stasis in this organ only when the pelvic level descended below the upper point of peritoneal fixation of the ureter. This point could be and was demonstrated several times. When sympathectomy was done, the ureter was stripped from the peritoneum as far down into the pelvis and as close to the bladder as could be reached from the incision. A bed was then made for the kidney in what should have been its normal position. The peritoneum and the lumbar fascia were stitched below this point so as to form a hammock to prevent the downward movement of the kidney and the patient returned to bed. Two weeks after the sympathectomy the patient developed a huge perinephritic abscess which was drained. This was probably caused by faulty technic, but the accident turned out to be a blessing in disguise.

It was found in a later study of this patient that the abscess had pushed the kidney down at least three inches below its normal position and here the kidney was absolutely fixed by the adhesions from the healing of the drained abscess. The ureter was no longer fixed to the parietal peritoneum so that it kinked; in short, the kidney was fixed in a very low position with a straight ureter, insuring good drainage. There was no pain because of the sympathectomy, nor was there any drag on the nerve supply, which accounted for the previous reflex gastro-intestinal disturbances. Stasis in the renal pelvis and the infection incident thereto was relieved, due to the loosening of the ureter from its fixation to the peritoneum. This straightening of the ureter is likewise due, I believe, to the greater strength of the circulatory musculature of the ureter, overcoming the action of the longitudinal fibers. This allows the ureter to shorten itself (an accordion-like collapse of the tube) and thereby prevents the kinking of the ureter that existed heretofore when fixed to a certain height by its attachment to the peritoneum.



After watching this patient for several years and seeing her return to her arduous duties as a school teacher, completely relieved of her suffering, it was believed that here was an operation that could be offered to the profession to take the place of the unphysiologic nephropexy with the kidney hooked to the twelfth rib.

Since then the operation has been performed several times, with success, where nephropexy heretofore was considered necessary. Naturally, other little features have been developed in the pre- and postoperative care of these cases which have seemed to be of great value. This physiologic nephropexy is offered to you with the feeling that if you will follow the technic carefully, you will be successful in the management of these cases.

#### TECHNIC OF THE OPERATION

The kidney is exposed as in any other renal operation and is delivered into the wound. If the organ has a long pedicle and can be easily handled with the hand, the operation is reasonably easy. However, if not, a long strip of gauze is placed around the pedicle, hooking it under the upper and lower pole and bringing the long ends up on the opposite side. In this manner the kidney can be retracted and held steady in any position, thus easily exposing the pedicle.

The sympathectomy may be carried out in one of two ways. The main trunk of the sympathetic nerve can be easily found running along the superior border of the renal artery. It may be easily picked upon a hook or grooved director and cut once, or beginning at the kidney pelvis, the fatty tissue surrounding the pedicle may be carefully incised. Then this adipose tissue, containing the nerve and its various filaments and the lymphatics, may be stripped off the vessels, pelvis, and upper ureter by gently brushing with a strip of gauze on the end of the index finger towards the mid-line.

After this has been done fine nerve filaments will be seen running along the vessels. These are picked up on a grooved director and cut. Cutting them on the grooved director protects the vessels from possible injury. Again the adipose tissue around the pedicle may be carefully incised some distance from the kidney as near the mid-line as possible and then stripped off the vessels, stripping toward

the kidney instead of away from it. No matter which method is chosen the vessels must be absolutely dissected clean for at least three-quarters of an inch. The more thoroughly the vessels are cleaned of all tissue the more thorough will be the sympathectomy. Then the ureter is thoroughly loosened of all its attachments as far down into the pelvis as possible. Some men have called this sympathectomizing the ureter but this is not a correct name for this procedure. Then a suture or two of chromic gut is placed below the kidney, stitching the peritoneum and lumbar fascia together. This acts as a hammock and aids in holding the kidney in the bed prepared for it. The incision is closed without drainage and a large pad of gauze is placed on the abdomen covering the lower abdomen below the umbilicus. This is held on by a reasonably tight abdominal binder.

The patient is returned to bed and for three days the foot of the bed is elevated. At the end of that time the binder is loosened and the foot of the bed gradually lowered. Before leaving the hospital the patient is rechecked cystoscopically and pyelographed.

In movable kidneys as well as in others, the kidney will be found to be fixed in a fairly high position by the surrounding adhesions. There will be practically no mobility. The ureter will be found straight and upon checking in the sitting or upright position the kidney will not descend nor will the ureter kink. As a matter of fact, if the kidney descends several inches before the adhesions form, and becomes fixed in a low position, it will no longer give symptoms. It does not really matter just where the kidney becomes fixed post-operatively just so it is fixed and its ureter is straight and not kinked.

*Conclusion.*—It may be said that renal sympathectomy is a very useful operation in renalgia, early hydronephrosis, and in dystopia with renal and gastro-intestinal disturbances. It has been successful in anurias, essential hematurias, and some cases of parenchymatous nephritis in the hands of others who have taken up the procedure.

It may be useful in other types of nephritis and grave hypertension, although no clinical application has as yet been attempted in these cases. It has never been successfully used clinically in renal tuberculosis.

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# Diagnosis and Treatment

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## THE MALARIAL THERAPY OF PARESIS\*

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Although before the introduction of malarial therapy at St. Elizabeths Hospital, all cases of paresis were receiving active and continued arsphenamin therapy, as may be seen from the various cases cited below, no appreciable clinical benefits were observed as a result of such treatment. A diagnosis of paresis was practically a death warrant and most of such cases were dead within three years following their admission to the hospital, as may be seen from the graph comparing the mortality in a group of patients who received malaria with those who received arsphenamin treatment. Of 214 consecutively admitted cases of paresis, before the introduction of malarial therapy, all but twenty-six were dead at the end of three years.

In the group of improved cases, some of which are cited below, a number had received extensive arsphenamin therapy before the inoculation and some have continued to receive arsphenamin even after the inoculation. This, however, was only continued during the first two years following the introduction of malarial therapy, but during the past four years those successfully inoculated with malaria received no other treatment except for a small group of cases used as controls.

The entire group of successfully inoculated cases was studied as to the number of patients who received anti-luetic treatment before inoculation and those who had no other treatment. Only a small number of those inoculated during 1922 and 1923 were given some intravenous treatment after the inoculation.

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\* The first portion of this important paper will be found in the September, 1931, volume of the *INTERNATIONAL CLINICS*.

Malaria-treated patients who also received arsphenamin did not show any greater results than the inoculated cases who received no other treatment. This is brought out in Table IV.

TABLE IV

*Analysis of the Entire Group of Successfully Inoculated Cases with Reference to Previous Treatment Received (Sulpharsphenamin)*

Group	Unchanged	Improved	Progressive	Died
Total in each.....	14	140	20	18
Received previous treatment.....	0	38	8	8
No previous treatment received....	14	102	12	10

While most clinicians seem to agree that malarial therapy produces definite beneficial changes in the clinical course of paresis there is still a difference of opinion as to how these beneficial changes are brought about.

Sufficiently large groups of successfully inoculated cases of paresis have not, as yet, come to autopsy and study by individual pathologists.

Some of the cases that did come to autopsy were cases inoculated in the very advanced stages or where death was due to many complications. Very few cases of clinically arrested or cured paretics have so far come to autopsy and it is only from study of such cases where death is due to some acute condition, not involving the central nervous system, that definite deductions could be arrived at from the study of such brains.

Most of the pathologists, however, agree that malarial therapy causes a regression of the pathologic process and the lesions become stationary. Some workers find the inflammatory exudate undergoes qualitative changes. Their interpretation is that the pathologic process has a tendency to change into a more benign form with a tendency toward the formation of the specific granulomatous lesions.

Kirschbaum<sup>5</sup> objects to this interpretation and expresses the opinion that malaria acts by a simple reduction and moderation of the inflammatory exudate.

According to Freeman,<sup>6</sup> during the early stages of treatment the

paretic process is exaggerated and he found a striking tendency toward organization of perivascular exudate. This early organized perivascular exudate later begins to show a progressive reduction in its volume with gradual disappearance of the cellular elements.

Spielmeyer,<sup>7</sup> however, does not agree that there is an early exacerbation followed by healing inflammation but emphasizes the degenerated state of the infiltrative cells and suggests the possibility that the fever may be the cause of the gradual disintegration of the exudate.

Ferraro's<sup>8</sup> observations are based upon studies of brains from twenty-nine patients treated with malaria who died at intervals after inoculations from five days to twenty-six months.

He calls attention to the fact that the pathologic process of paresis is not uniform and absence of inflammatory changes following malaria may mislead one to suppose that this was the benevolent result of the malarial inoculation, whereas they may have been absent before the inoculation.

Mildness of exudative process may not necessarily be due to malaria.

Ferraro<sup>9</sup> does not agree with Freeman that there is an organization of exudate as a result of malarial treatment, but maintains that organized exudate is the most usual finding wherever there is true inflammation. He<sup>10</sup> believes that malaria acts primarily on the inflammatory process favoring its gradual re-absorption. He quotes von Lehoczky<sup>11</sup> who emphasizes that the action of high and prolonged temperature causes a degeneration and disappearance of inflammatory cells. Ferraro's conclusions are as follows:

"Malaria influences favorably the pathologic changes. It consists in diminution of exudate and reduction of the new blood-vessels. Influence on parenchymatous changes is less definite.

"No parallelism exists between re-absorption of inflammatory exudate and the clinical course, but there is a rough parallelism between clinically favorable cases and subsidence of some of the exudative reaction.

"There is no secure way of establishing a comparison between the intensity of the process in general, prior to malaria, and the effect which the treatment has on it. The less pronounced, however,

the parenchymatous changes, the higher are the chances of clinical improvement."

Ferraro's observations would tend to explain why in studying the results of our cases, from each of the three levels of the disease, we find less pronounced changes at the neurologic level. Excitements, flight of ideas and such symptoms as tremors, the milder speech defect and the disturbances in finer coördination may be principally due to inflammatory lesions which are especially influenced by the treatment; but such symptoms as rigid pupils, pronounced speech defects, absent knee jerks and the mental symptoms suggesting the demented and deteriorated types of paresis are primarily due to parenchymatous changes and are less favorably influenced.

#### CLINICAL RESULTS

##### *Group One. Social Recoveries.*

Twenty-five patients were discharged from the hospital as social recoveries.

Such patients upon discharge from the hospital were free from mental symptoms and had a good appreciation of their former mental states. They were in good general physical health, neurologic symptoms were mild and most noticeable upon ordinary observation. Serology was either entirely negative or nearly so. Such patients had no evident handicaps and in most instances were able to resume their former occupations with the same degree of efficiency as before their illness and a few patients received promotions and made progress in their respective occupations as though they had never been ill with paresis. Such results were never known before the introduction of malarial therapy.

Attention must also be called to the fact that most of the cases discharged as social recoveries were under hospital supervision for several years and their successful social and economic adjustment continued without any interruption for reasonably long periods and at the time of this report there is no apparent reason why this satisfactory condition should not continue indefinitely.

##### *Group Two. Improved.*

Fifteen patients were discharged from the hospital improved. Such patients were usually free from active mental symptoms,



had been able to make excellent institutional adjustments with only nominal supervision and their everyday behavior did not show anything strikingly unusual. There were, however, definite residuals at the mental and neurologic levels. In most instances they could not resume their former occupation if it required considerable mental alertness. They presented however no behavior problems. Under ordinary family supervision they were able to make good extra-mural adjustments, making themselves useful about the house or farm or following such occupations as watchmen or messengers or collectors.

*Group Three. Improved cases who remain in the Hospital.*

This is rather an extensive group consisting of 141 patients. This group may be divided into the following sub-groupings:—

A. Patients forty-five who were almost social recoveries but who remained in the hospital because they have neither friends nor relatives who could assist them toward social and economic rehabilitation. Many of such patients formerly served in the various branches of the military service and being without trade or profession could not hope to reestablish themselves without some assistance. In the hospital, however, their behavior is without any abnormality. They are usefully employed, enjoy ground and city parole and behave like normal citizens.

B. Patients fifty-two showing varying degrees of emotional and intellectual dulness but without any active mental symptoms. These are usefully occupied at the hospital many having ground and city parole and require merely nominal supervision.

C. Patients thirteen showing marked emotional and intellectual deterioration to the point of vegetative existence but whose condition is arrested and under ordinary hospital care present no special problems of management.

## PART II\*

### SOCIAL PROBLEMS

That paresis presented many complicated sociological problems has long ago been recognized by the medical profession at large and particularly by the psychiatrist.

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\* Material prepared and put together by Dr. J. E. Lind.

The failure of early diagnosis of paresis not infrequently led to most disastrous results when the victims of this malady were individuals holding important public offices such as high government officials, heads of large banking institutions, presidents of important industrial corporations, insurance companies, members of the diplomatic corps and people upon whom the safety and welfare of others depended such as captains of passenger vessels, locomotive engineers and others holding positions requiring the highest degree of mental alertness and most discriminating judgment.

All the above, however, were problems of the incipient stage of paresis; problems of prophylaxis. Once a definite diagnosis of paresis was made most of the social problems created by the disease, at least as far as they involved the responsibility of the psychiatrist, were fairly easily dealt with, though less satisfactorily, perhaps, from the standpoint of the individual patient. A diagnosis of paresis once established, institutional commitment was invariably advised and if the patient was permitted to remain at his home he was declared mentally incompetent and was removed from any activity which required executive capacity and intellectual effort.

As far as the institutional psychiatrist was concerned the social problems created by the paretic patient did not tax to any great extent either his professional efforts or diplomatic tact with relation to the patient or his relatives.

Here at St. Elizabeths Hospital the procedure was rather simple. As soon as the serologic reports confirmed the diagnosis a letter, with a few minor variations, was sent to relatives, as follows:—

"I regret very much to have to inform you that as a result of a very careful examination of your son's (or husband's) case, including that of the blood and spinal fluid, we have come to the conclusion that he is suffering from a very serious organic disease of the brain which is considered by the medical profession to be incurable.

"During the course of this disease attacks of convulsions are apt to occur, and while recovery may follow some attacks others are apt to end fatally.

"While temporary improvement is possible sooner or later the course of the disease is downward, *etc., etc.*"

In the cases where there was temporary improvement and the

patient continued to live in a comfortable state for a number of months limited ground parole and later full ground parole was possibly granted but rarely indeed was a parietic granted city parole. Many of the parietic patients were dead within from four to five months after admission; more than fifty per cent. were dead at the end of the first year and at the end of three years after admission only a very small number remained alive.

In the few rare instances where a parietic was removed from the institution it was always against medical advice and the relatives would soon be obliged to return him and would feel quite contrite that they even dared question the gloomy prediction of the specialist and as far as the hospital was concerned there were no other social problems to meet.

Malarial therapy has changed most of the conditions described above and has raised many, and at times quite taxing problems. We can no more state that the disease is incurable and it would be dangerous to prognosticate the patient's duration of life. In writing our initial letter to relatives after a diagnosis of paresis is made we still state that the patient is suffering from a serious disease of the brain, and then proceed to say that until recently the disease was considered to be incurable but that a new method of treatment now in use may produce beneficial results.

When after a period of six or more months the patient or his relatives request his discharge we no more arbitrarily refuse it or even advise against it. Until now, however, our position has been a more or less passive one. However, as the effects of malarial therapy become public knowledge we will be obliged to take a more positive stand and the patient and his relatives and the public at large will seek and demand of the psychiatrist more positive guidance.

Recently we admitted a number of patients who came here principally for the malarial treatment and not because of any anti-social behavior.

What then are some of the newer problems confronting us?

1. Diagnosis.
2. Prognosis.
3. Is the disease contagious or infectious?

4. Shall we inform the relatives or wife of the nature of the disease?
5. Legal problem.
6. Custodial problem.
7. Question of disability.
8. Permission to drive an automobile.

## 1. Diagnosis.

The importance of making a correct diagnosis needs hardly any special emphasis. During the pre-malarial era it occasionally happened that a patient was erroneously diagnosed paresis. Subsequent serology or his improved mental and physical condition would result in the change of diagnosis. Such a patient and his family could be assured that he never had paresis. Under malaria this is more complicated.

Should a patient be erroneously diagnosed paresis and given malaria subsequent clearing up of symptoms and even negative serology would naturally be attributed to the treatment. So while it is desirable to start the treatment as early as possible we should be very careful in making a diagnosis of so-called early paresis or basing the diagnosis on the serology alone. Certainly no treatment should be started until all doubt as to the diagnosis has been removed. Our own opinion is that a colloidal gold reaction of 55555 in the absence of some characteristic mental and neurologic symptoms, especially the latter, does not justify a diagnosis of paresis. We have now a number of patients tagged paresis who are not paretics though most of them do have syphilis of the central nervous system.

## 2. Prognosis.

What should be our attitude in this respect? It is unnecessary here to emphasize that each case will necessarily present special individual problems, but I am concerned with our prognostic attitude in the light of changed conditions. Based on results given above the general prognosis should be of a hopeful nature and the degree of involvement of the neurologic level may act as our prognostic guide. The less prominent the neurologic symptoms the more beneficial may be the result. In the cases of patients who

follow ordinary trades or occupations not involving the handling of finances or in the cases of those holding positions not requiring any special intellectual effort or critical judgment—return to work may be held out as a possibility within a period of six or more months.

3. Is the disease contagious or infectious?

This question is being propounded with more frequency and more persistency by the patient and his relatives, especially the wife. We allow our paretic patients to work in our kitchens, dining rooms and mix them with our other patients. So we can hardly regard paresis as contagious. What the questioner, however, wants to know specifically about is concerning conjugal relations and whether it is safe for them to have children.

Recently one of our discharged paretic patients became engaged and the girl discovered her fiance had been a patient here and she asked a number of specific questions. The questions were evaded on the ground that the information was of a confidential character. During the pre-malarial era such questions did not arise. Likewise a number of our paretic patients were sued for divorce and the patients and their relatives sought specific information on the subject. Suppose we are subpoenaed to court in such cases as expert witnesses, what should be the nature of our testimony?

4. Shall we inform the relatives and especially the wife of a patient of the nature of the disease?

This applies not only to us here in Saint Elizabeths Hospital but perhaps more so to the various psychiatrists who deal with the patient before he comes here.

Recently we had a number of perplexing situations to deal with where this problem was involved. When the patient became ill and the diagnosis of paresis was established, the wife was told all about the nature of the disease and its probable duration before he was ordered to Saint Elizabeths Hospital.

Surviving the shock of such news the wife proceeded to make some sort of adjustment to such a difficult situation.

In some cases the home was broken up. The wife went to work or went to live with her mother or with the help of various social

agencies and often with the husband's pension or retired pay she was able to get along. After a number of months she became adjusted not only economically but also emotionally. However, in one case about a year later the husband became much improved and he insisted on going home to support his family. We wrote to his wife rather cautiously telling her of her husband's improvement and of his desire to go home on a visit. A very bulky letter, sent by special delivery, was received. The wife described in detail all the difficulties she had had with him before he was hospitalized, quoted the various doctors who told her that her husband was incurable, stated that his home coming would disrupt everything and finally ended with the admonition not to think of discharging him until he was completely cured. In some cases the situation is more complicated because the patient had been receiving quite regularly very solicitous letters from his wife telling him how much she hoped he would be able to come home real soon, and at the same time the wife requested the hospital not to divulge to him the content of her letters. There followed then an endless chain of correspondence and in some cases congressional pressure was brought about to keep the patient here.

#### Example of a Problem Case.

*F. M.*, aged 38, upon admission to Saint Elizabeths Hospital, November 4, 1928, was for thirteen years a civilian employee of the Canal Zone. He married there and acquired property. He was industrious, a law-abiding and a respected member of his community. He belonged to the Labor Union and also to various high type fraternal organizations where he was popular and had many friends.

About July, 1928, he began to show the usual change in personality, becoming irritable, extravagant and grandiose. In October, 1928, following an altercation with the police he was committed to the Insane Asylum in Corozal, where a diagnosis of paresis was easily established. The patient was apparently quite disturbed and strenuous efforts were made to transfer him to the States.

At first this hospital refused to admit him. It was suggested that he be sent to the state of his legal residence; Virginia, however, refused to accept him because he had been away from there

for thirteen years working for the government and Saint Elizabeths Hospital was again suggested. The Governor of Panama sent a letter to the Interior Department as follows:—"Referring to previous radios regarding insane patient M. is very violent. No suitable place here for caring for violent white insane and insufficient attendants without the use of negroes. Necessary to keep him in frame building with sixty-five other patients. On three occasions he has attempted to set fire to buildings. Transfer to U. S. extremely urgent."

Although there was considerable correspondence between various departments the transfer was effected within one month after his admission to Corozal. Here he was rather disturbed for about two months, being threatening and rather combative, but he soon began to improve and after four months' residence presented no more behavior problems. The patient received two malarial inoculations without any result. It is interesting that he had had two natural attacks of malaria some years before the onset of his illness and while waiting for the third inoculation and having quieted down he wrote a letter to the Superintendent requesting that he be sent back to the Canal Zone where he said he would have no trouble securing blood from a malarial patient. However, in May, 1929, he had a third inoculation followed by eight paroxysms which were stopped by quinine. There followed steady improvement and he was able to enjoy both ground and town parole and worked efficiently in our upholstery department.

In December, 1929, he was allowed to visit his sister in Virginia where he did very well and returned to the hospital in March, 1930.

His behavior in the hospital for a number of months was quite normal. He had good insight and his judgment was unimpaired. During his entire period of absence from the hospital reports from relatives indicated that his conduct was in all respects quite normal.

During 1930, he was away from the hospital most of the time, returning to the institution for reëxamination and serologic check-ups.

He worked for several months in a town in Pennsylvania, receiving the usual wage of a pipe-fitter. In May, 1930, when he reported to the hospital for a serological check-up there was no evidence of any mental symptoms and the serology was practically

negative. The colloidal gold reaction in August, 1930, was 122211000; Kolmer (10000) doubtful; Protein—zero; Cells—two.

A psychologic examination, performed by Dr. Richmond in May 23, 1930, gave the following results:—"Very normal in appearance and manner and nothing appeared during the examination of an hour and a half to indicate that he is not in his normal state now. He uses a good vocabulary; discusses his situation intelligently. He was unable to repeat six digits forward and backward beyond a ten-year level which could indicate a lack of ability of attention or some memory loss though his memory in other respects appears good. His final score was fourteen years and three months which is good average intelligence. He shows far less scattering than the average malaria treated parietic."

He was declared competent and of sound mind for certification to the Canal Administration so that his property could be released and he was again permitted to go on a visit on August 16, 1930.

While at Corozal Hospital the wife of this patient was told all about the disease and after his admission to Saint Elizabeths Hospital we wrote her that he was suffering from a very serious form of organic brain disease from which complete recovery is a matter of great uncertainty, and then mentioned that of recent years a new treatment had been instituted which promised some encouraging results. There followed a number of letters in which his condition was described as unchanged but after the successful inoculation the wife was told the patient was improved, but her attention was again called to the seriousness of the disease.

Early in 1930, the patient's wife was informed through several letters of his progressive improvement, his excellent hospital adjustment and his visits to his sister's home.

To a subsequent inquiry on the part of the wife whether the patient was a cure and how long it would be necessary for him to remain in the hospital, we replied that it was difficult at that time to state whether he would ever be cured and advised his remaining at the hospital for an indefinite period to enable us to tell whether the patient's improvement would remain permanently.

To the above letters the wife replied that she quite agreed to his remaining at the hospital and that she would not consent to his release until he was cured.



In March, 1930, the patient's wife wrote another inquiry about his condition stating "I still feel that he should stay at your hospital until cured." She mentioned that unless he was a complete cure he could not get his government job back and stated that regardless of how much she would like to have him with her, she thought it would be foolish for him to leave before he was cured. To this we replied that if we are to wait until we could say that he was completely cured he might have to stay here the rest of his life. We explained at length his condition, stating that he had been normal mentally for almost a year and suggested that he might go on a visit to the Canal using a government transport which would be inexpensive and to which he was entitled by reason of his service in the Canal Zone. This would give his former employers an opportunity to size him up and should he fail in his adjustment he could return to the hospital or live with one of his sisters in Virginia who was quite anxious to have him there. We then received a letter from his wife in which she stated that she had referred our letter to the Executive Secretary, The Panama Canal, as to whether the return of the patient would be permitted. This matter was in return referred to the Superintendent of Corozal Hospital for the Insane and the chief health officer of the Panama Canal whose opinion is quoted below:—"Records show *M.* discharged from Corozal October 28, 1928. Diagnosis, general paralysis of the insane. No improvement at the time of his transfer to Saint Elizabeths. In view of the diagnosis in this case and further fact that the patient unquestionably had symptoms of a severe psychosis it is recommended that the return of Mr. *M.* to the Canal Zone be disapproved." (Signed) — Superintendent.

The Health Officer concurred with the above opinion.

Based on the above opinions the executive officer wrote to the patient's wife:—"Mr. *M.* could not be admitted to the Canal Zone on the advice of health department authorities."

The wife then emphasized that he must not be released until cured. She complimented the hospital for the improvement achieved so far and again mentioned how much she would like to see him discharged. The patient in the meantime visited the local Canal office in an attempt to straighten out his finances which were in the hands of the Canal administrator. At about this time action

was instituted in the Canal office to have a guardian appointed for the patient although the patient had been normal mentally for over a year. The hospital finally received an inquiry from the Canal authorities of this city which was initiated by the Governor of the Canal. We reported the patient's condition stating that he could be discharged from the hospital at any time upon his request and declared him competent to take care of his property.

On October 12, 1930, we received the following interesting letter from the patient, who was at that time in Virginia with his sister: "I received my estate from the Administrator of Estates of the Panama Canal and am very grateful to you and Saint Elizabeths Hospital for the care and consideration shown me while there. I have another problem at present I would like your advice on. Mrs. M. was here on a short visit last week and wants me to arrange for a divorce as she feels she cannot possibly live with me on account of the disease. I would like to know for my own satisfaction if this disease is still in a contagious condition. I am getting along very well here, working every day installing heating plants; feel very good. My weight is remaining just the same—178 pounds. Thanking you again for all you have done for me."

There followed a postscript: "There does not seem to be any likelihood of my returning to Panama at present for the authorities there don't seem to think I am well enough."

It would appear that in this case the medical profession made every possible attempt and practically succeeded in curing the disease but did not give sufficient consideration to the patient and his social problems and thus indirectly at least assisted in breaking up his home.

## 5. Legal Problem.

Practically 100 per cent. of the paretic patients are adjudicated through the courts and guardians take charge of their property.

After a patient has been successfully inoculated with malaria, and begins to show improvement neurologically and serologically and is free from any mental symptoms how long should we wait before certifying him to the court as recovered? In this connection it may be recalled that in June, 1926, Saint Elizabeths Hospital for the first time reported a case of paresis to the court as recovered.

The patient in question after being inoculated with malaria showed marked improvement at all levels and for over a year lived outside the hospital, his behavior being normal, and repeated examinations failed to bring out any evidence of mental symptoms.

In order to liquidate certain investments which the patient made before he became ill it was necessary for him to remove his legal disability. The question came up whether the hospital could certify him as recovered. It was decided to put this problem before the Interior Department and the solicitor of that department was consulted. The result was a letter from the first assistant secretary as follows:—

“Reference is made to the case of *F. C.* now confined as a District patient in Saint Elizabeths Hospital under existing laws and whose discharge is sought on the grounds that at the present time he is of sound mind. You state that Mr. *F. C.* is a victim of paresis and that this disease is incurable but that at present time he is of sound mind and is permitted to live at his home in the District with his sister under indefinite parole, that he visits the laboratory of the Saint Elizabeths Hospital and performs some work therein and thereafter returns to his home. It is further stated that he is competent and able and is looking after business matters for his sister. In other words, that while at some time in the future, which time you cannot fix definitely, his release may cause a recurrence of his mental ailment, at the present time he is of sound mind and competent to look after himself and transact business.

“Assuming this to be a fact, I see no reason why the superintendent or the acting superintendent of the Government Hospital for the Insane cannot properly and lawfully make the certification provided for in Section 2 of Act of Congress, approved February 23, 1925, and covered by your form No. 1-456.

“You will note that the Act of Congress cited and the Form No. 1-456 does not require you to certify that the insanity will never recur. The Act requires the superintendent to file his statement that such person in his opinion was at the time of his discharge of sound mind.” (Signed) E. C. Finney, first assistant secretary. The patient was accordingly certified to the Court as “recovered as of June 22, 1926.” In October, 1928, when the survey of the malaria-treated paretics was completed this man was still in excel-

lent shape and had been continuously and successfully engaged in the real estate business.

#### Problem 6. Custodial Problem.

In the cases of arrested paresis but with a moderate degree of organic deterioration which would make it difficult for the patient to make an economic adjustment or in cases of the ex-Navy or ex-Army men without pensions and who are without any trades should such patients be retained in institutions indefinitely or be sent to Soldiers' Homes or other Custodial Institutions? As time goes on we will have more and more paretics whose condition is arrested and who merely require a lodging place.

#### Problem 7. Question of Disability.

This problem is concerned with rating of patients for the Veterans Bureau and for government and private insurance companies. Heretofore such cases were rated as permanently and totally disabled. Should we not treat the patient first and then give a prognosis?

#### Problem 8. Permission to drive an automobile.

Finally there is the perplexing question of driving a car. Should paretics whose condition is arrested be permitted to drive?

We realize that all the above problems cannot be satisfactorily solved at this time for the simple reason that we have not yet accu-

TABLE V

*Relationship of the Duration of Paresis Prior to Malarial Treatment to Therapeutic Results*

Duration of Paresis Prior to Treatment	6 Months	12 Months	24 Months	36 Months	Over 36 Months	Total
Total number of cases treated.....	105	51	21	16	16	209
Number of benefited cases.....	85	37	11	11	6	150
Per cent.....	80.5	72.5	52.3	68.7	37.4	71.5

Difference in Percentage of Improvement—Early 80.5 Per Cent. against Late Cases 37.4 Per Cent.

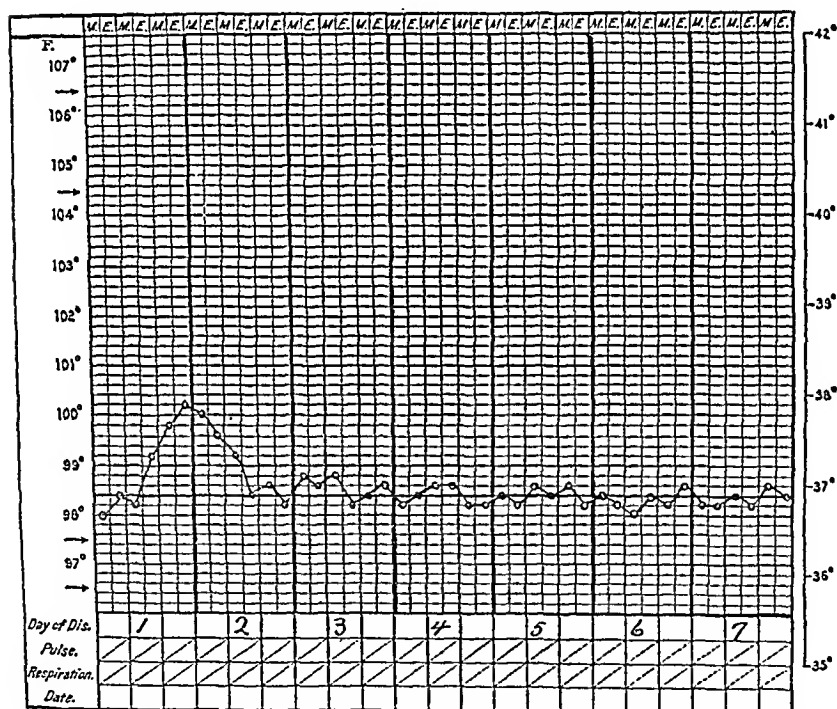
mulated sufficient experience to guide us in their solution but I felt it worth while to set them forth hoping that their discussion would be profitable and helpful to those who must handle such problems almost daily in a very concrete and practical manner.

### THE TECHNIC AND DETAILS OF THE TREATMENT<sup>12</sup>

Benign tertian malaria was selected because it offers best results and because of the ease with which it can be controlled.

CHART I.

Showing Temperature Reaction from Introduction of  
Inoculation Blood Few Hours After Inoculation.



Many hospitals in this country maintain malaria strains by direct passage from patient to patient in those under treatment. This, of course, is not without some risk and at Saint Elizabeths Hospital it was decided in the beginning that no possibility of any error (diagnostic or otherwise) could be permitted and therefore all paretics have been inoculated with malaria from non-luetic donors.

This necessarily results in delays and large groups of patients must be inoculated at a time. Some patients must go without treatment for many weeks.

At Saint Elizabeths malarial blood is preserved by a  $\frac{1}{2}$  per cent. solution of sodium citrate.

*Selection of Patients.*—The best results are naturally obtained by treating early cases; but at Saint Elizabeths we decided to give the treatment to all patients and the first group of inoculated patients included those who had been in the institution for some time, and were in the very advanced stage of the disease—some being bedridden. The results obtained and which will be given later were obtained in non-selected cases.

*Technic of Inoculation.*—Type of blood of the donor need not be considered in relation to blood types of patients to be inoculated. In only a few patients were reactions observed but they were of such relatively mild character that they could be justly disregarded.

TABLE VI

*Showing the Relationship of the Method of Inoculation to Successful Results*

Method of Inoculation	Success		Failure		Total Number
	Number	Per Cent.	Number	Per Cent.	
Subcutaneous method.....	83	76.9	25	23.1	108
Intravenous method.....	124	72	48	28	172

It is important that the parasite in the donor be positively identified as the *benign tertian type*. Inadvertent use of a malignant type of malaria may result in fatalities before the parasite can be eradicated.

Best results were obtained if the donor had at least four or five severe paroxysms before the blood was used.

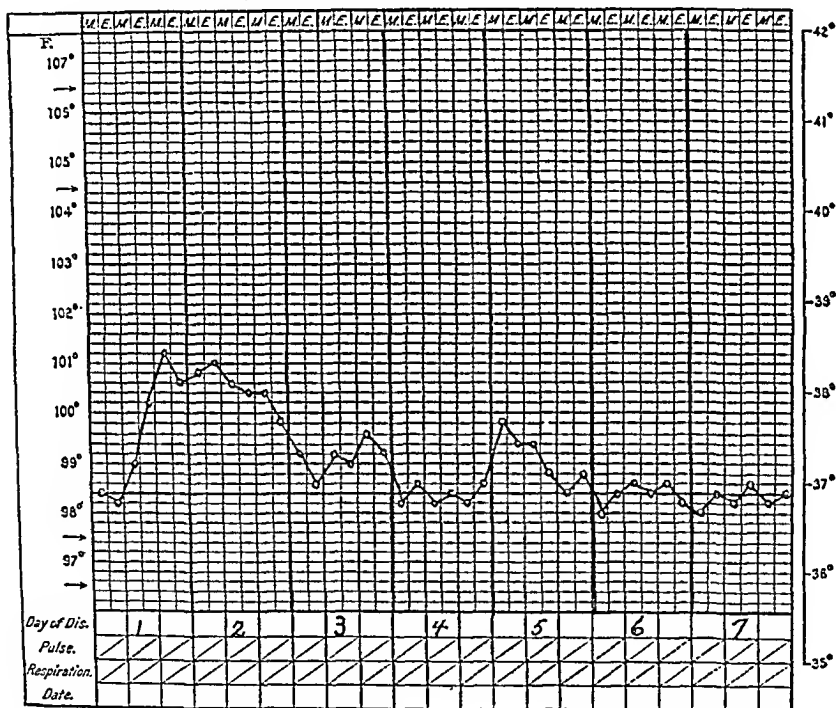
Two methods have been used, *viz.* (1) the subcutaneous and (2) the intravenous methods. The inoculation period is somewhat longer with the subcutaneous method but certainty of successful inoculation is somewhat greater than with the intravenous method. The subcutaneous method requires less blood; the technic is much

simpler and is accomplished easier and during the past few years the subcutaneous method has been used extensively.

*Subcutaneous Method.*—A needle of generous gauge, of about one and a quarter inches in length, is inserted into the loose subcutaneous tissue in the area of the angle of the scapula. Two or three cubic centimeters of blood are injected, a small amount in

CHART II.

Showing Reaction of More Severe Character Following  
Introduction of Inoculation Blood of Donor.



each of several directions radiating from the site of the puncture. This is for the purpose of spreading the blood over a larger area thereby increasing the likelihood of absorption and successful inoculation. After inoculation the wound is covered with sterile cotton and collodian dressing.

*Screening of Patients.*—Where malaria is not prevalent this is hardly necessary.

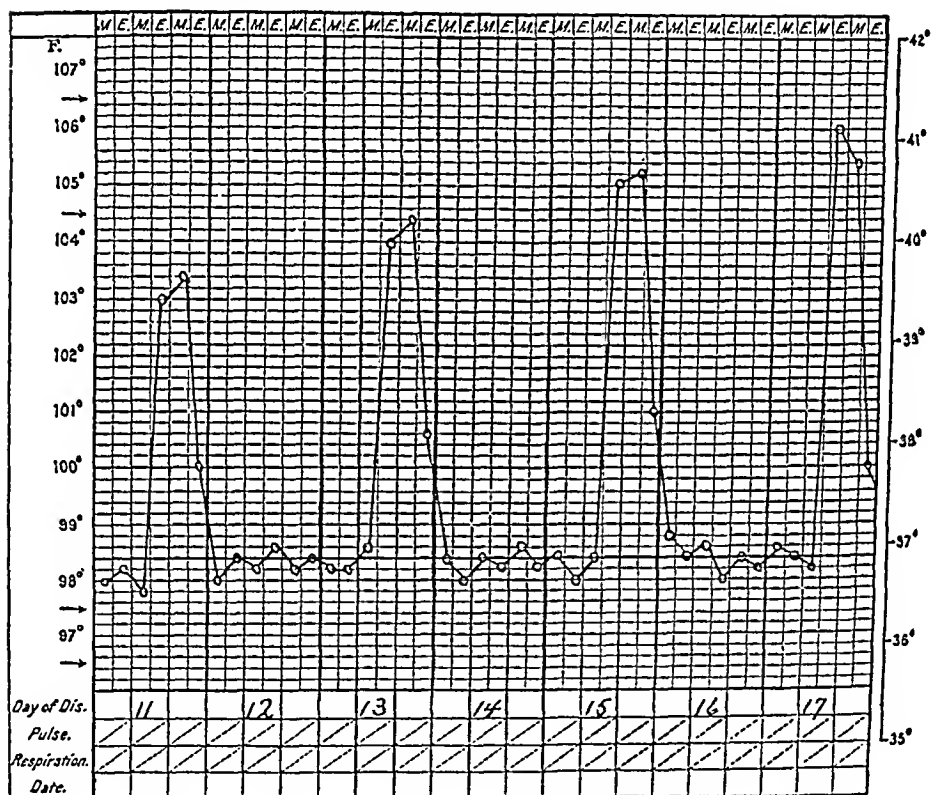
*Incubation Period.*—This is considered from the time of inocu-

lation to the appearance of the first malarial paroxysm. The inoculation period varies from five to forty-five days, with an average of fourteen days in the subcutaneous method. If no paroxysm is manifested within three weeks it is regarded a failure and if malaria is available such patient is reinoculated.

Very few patients who do not have a successful initial inocu-

CHART III.

Showing Periodicity of Single Tertian Infection.



lation will react to subsequent inoculation. This is particularly true of the colored race.

In a small number of cases a moderate rise of temperature,  $101^{\circ}$  to  $102^{\circ}$ , will occur twenty-four hours after inoculation accompanied by malaise and headache but will subside during the next twelve hours. After the second day it is unusual for any patient to exhibit any manifestation. Temperature Charts I and II show such initial reactions. After inoculation the temperature is recorded every four hours to the time of the completion of the treatment. The patient

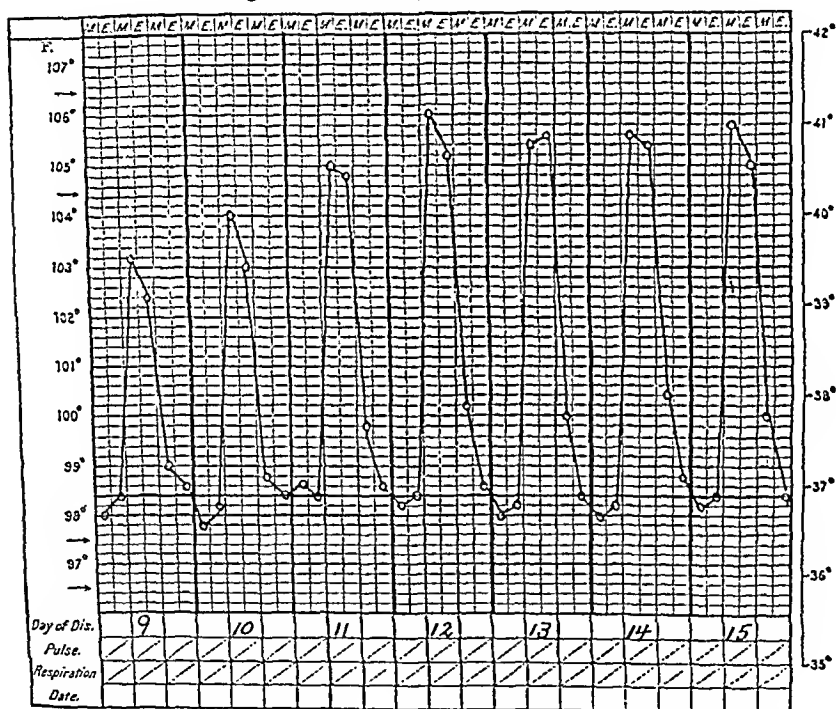


is watched for the occurrence of each chill and his temperature is taken as soon as possible after its subsidence. Temperatures usually range between  $104^{\circ}$  and  $106^{\circ}$ . Temperature Charts III, IV and V illustrate different types of periodicity, *viz.*, single tertian, double tertian and irregular.

We disregarded every fever rise unless it was preceded by a chill.

CHART IV.

Showing the Periodicity of Double Tertian Infection.



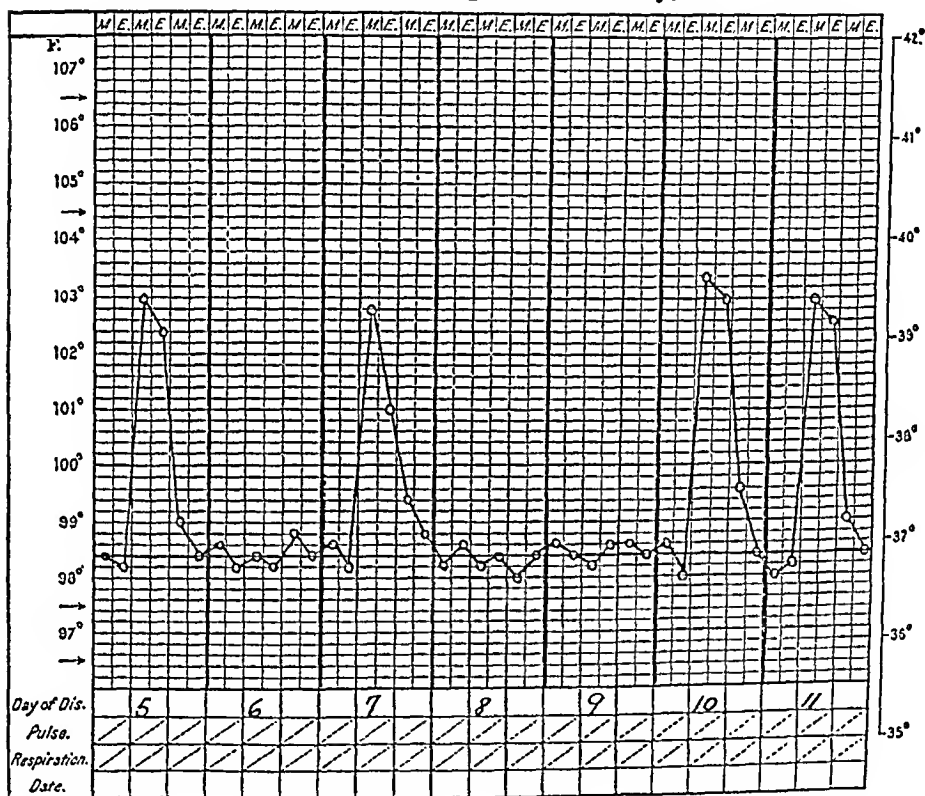
Convulsions are apt to occur in patients who previously suffered from them but this is not necessarily of serious concern. If the patient, however, had no previous convulsions their occurrence after inoculation requires special vigilance for the cardiovascular system and if the heart cannot be supported by caffeine, sodium benzoate, and digitalis, malaria should be aborted at once by intravenous injection of quinine hydrochlorid.

Jaundice is seen occasionally but only rarely is the spleen enlarged and then not to any great extent.

Usually if there are no complications at the outset of clinical malaria no further difficulty is experienced.

Absence of fever after a chill is regarded by some as a serious sign of impending collapse. Such patients are watched carefully and, if necessary, malaria is aborted. In our experience this has not occurred. During the first two or three years of our experience

CHART V.  
Showing Irregular Periodicity.



we tried to let each patient have from fifteen to eighteen paroxysms. Lately we have regarded twelve to fourteen a sufficient number, but recent European workers reported especially good results with eight paroxysms. If this number is shown to be sufficient it will facilitate the treatment as the patient will not become exhausted, the loss of weight will be lessened and the period of care much shortened. Where the fever, however, is not above  $104^{\circ}$ , a greater number of paroxysms is desirable.

Best results were obtained where the periodicity following inoculation was of double tertian type. In such cases fever was higher,

number of paroxysms greater and there was less tendency to spontaneous subsidence.

The higher temperatures occurred in patients with greater number of paroxysms and quinine usually had to be given to stop the paroxysms. Such cases gave the best results. The height of the fever and the greater number of paroxysms were not dependent entirely upon virulence of the parasite but upon reactive power of the patient.

#### CARE OF THE PATIENT AFTER INOCULATION

Initial reaction within twelve hours after inoculation may occur but it is usually mild and requires little treatment. Temperatures are taken every four hours and should be taken as soon as possible after the chill. A high temperature without a chill is not regarded as a paroxysm for therapeutic purposes. It is not considered necessary to confine patients to their beds following inoculation.

*Convulsions.*—These usually occur in patients who previously suffered from them, in which case such a phenomenon is not regarded as especially serious but the patient must be watched closely. If convulsions, however, occur in patients who were free from such, prior to inoculation, this is regarded as a complication and the cardiovascular system must be watched. If the heart does not respond to caffeine and digitalis, quinine hydrochlorid should be administered intravenously and malaria stopped at once. Such a patient may be able to undergo a successful inoculation without any complications two or three months later.

TABLE VII

*Relation of Method of Inoculation to Type of Periodicity*

Method of Inoculation	Tertian Type	Double Tertian Type	Irregular Type	Total
Subcutaneous method.....	23	47	13	83
Per cent.....	27.5	56.8	15.7	100
Intravenous method.....	30	60	34	124
Per cent.....	24.1	48.2	27.7	100

Patients should be kept in bed at least twenty-four hours during each paroxysm and chilling of their bodies should be prevented.

*Jaundice.*—Jaundice has been observed in some cases after inoculation. In most cases it is only of mild degree. The spleen is only occasionally enlarged, and then only in moderate degree.

None of the above have proved to be serious complications in our series of treated cases and no special treatment was required. Usually if no complications develop at the outset of clinical malaria the subsequent course is quite uneventful. Occasionally some patients will show symptoms of approaching collapse after the fifth or the sixth paroxysm. In such cases one or two grains of quinine by mouth will interrupt the paroxysms but not entirely abort them. Two or three paroxysms may be eliminated and the patient's general condition improves in the meantime. Should this fail to take place it is then best to immediately abort the malaria with full doses of quinine.

*Type and Number of Paroxysms.*—The periodicity of malarial paroxysms following inoculation does not occur every other day as in the naturally acquired malaria. About 30 per cent. of cases exhibit a true tertian periodicity. Thirty to 40 per cent. show daily paroxysms as though the patient had a double tertian infection. The remaining 30 or more per cent. of cases show an irregular type of periodicity. Two or three paroxysms may occur every day, a fourth paroxysm two or three days later, a fifth on the following day and others may continue with similar irregularity. In cases showing this irregular periodicity there is a tendency for the paroxysms to subside altogether without the administration of quinine and this subsidence may occur after any number of paroxysms. Table VII is interesting as it shows the relation of the method of inoculation to type of periodicity. Irregular type of periodicity results in lesser number of paroxysms and a lesser number of cases will show high temperatures. The double tertian periodicity on the other hand gives greatest number of paroxysms and highest temperatures. This may be seen from the study of the table on the next page showing relationship of the temperature peaks to the type of periodicity.

When the type of periodicity, number of paroxysms and height of fever are considered in relation to the therapeutic results the conclusions are as follows: Patients having an average temperature

Temperature	Types of Periodicity		
	Tertian, Per Cent.	Double Tertian Per Cent.	Irregular, Per Cent.
102°.....	0	33.3	66.7
103°.....	21.8	31.3	46.9
104°.....	21.4	50.0	28.6
105°.....	28.8	57.6	13.6
106°.....	27.7	57.6	14.7

between 104° and 105° will be more likely to have the requisite number of paroxysms of the double tertian periodicity with the greatest degree of improvement.

This group of cases shows a small percentage of subsidence of the paroxysms without quinine—namely, only 12 per cent. against 32 per cent. in the tertian periodicity and 49 per cent. in the irregular type. Best therapeutic results are therefore obtained where the patient has ten to twelve paroxysms which must be stopped by quinine when the temperature reaches about 105°.

*Inoculation Failures.*—Among white patients 5 per cent. to 10 per cent. of inoculated cases failed to develop any paroxysms at all and of the colored 80 per cent. to 90 per cent. have shown the same result. Only a small number of cases reacted to a second inoculation and only occasionally to a third one but after a third attempt it appears useless to keep on trying and diathermic treatment is the method suggested.

*Malaria Deaths.*—The death rate in the group under study traceable directly to malaria has been 4.3 per cent. of all inoculated cases. It must, therefore, be frankly recognized that the treatment is not without some attendant danger. This diminishes, however, in direct proportion to the method of selecting cases for treatment. As has been previously stated, when it was decided to try this method of treatment our cases were not selected. Every parietic in the hospital was inoculated and many of the cases had been in the institution for a number of years. Two were in the extreme stage of the disease. Many were considered very poor risks at the time of the inoculation. If inoculations were limited to cases in fairly

good general physical state the mortality rate would be very low and no deaths at all might follow.

*Repetition of Treatment.*—In a few cases successfully inoculated but who failed to show clinical improvement another course of treatment was tried but the results were unsatisfactory. Some could not complete the treatment and in those cases in which the second course was successfully carried out no improvement was observed but on the contrary the deteriorating process seemed to be accelerated.

We have therefore come to the following conclusion: One course of treatment consisting of not less than ten to twelve paroxysms with an average temperature peak of  $104^{\circ}$  or more will produce the maximum result that can be expected from malarial therapy.

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# THE RÔLE PLAYED BY HELMINTHS IN THE PRODUCTION OF TUMORS IN MAN AND ANIMALS

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THE rôle played by certain helminths in the production of different neoplasms in man and animals is a subject of some interest at the present time, and one about which further investigations are desirable. Fibiger's investigations have demonstrated that gastric carcinoma in rats may often be brought about from infection with the nematode *Gongylonema neoplasticum*. By feeding rats with cockroaches of the species *Periplaneta americana* harboring the encysted larval forms of *Gongylonema neoplasticum*, gastric carcinoma has also been produced. For his studies on the parasitic causation of neoplasms, with particular reference to carcinoma, Fibiger was recently awarded the Nobel prize in medicine. His work upon *Gongylonema neoplasticum* has been confirmed particularly by the investigations of Wassink and Yokogowa. We now recognize that at least three rat tumors, a hepatic sarcoma, a gastric carcinoma, and a carcinoma of the bladder may be brought about through the agency of, or in association with, helminths.

In this connection, it may be recalled that the parasitic theory of carcinoma is one of the oldest hypotheses of the origin of malignant tumors. Such a theory appears to have appealed to the ancients, was generally accepted in the Middle Ages, and definitely advanced by many modern observers. It reached the height of its popularity as a theory about 1895. However, as Ewing has pointed out, during the last fifteen years it has rapidly lost ground and today few competent observers consider it as a possible explanation of the unknown element in the production of true neoplasms. Nevertheless, while the idea that a specific cancer parasite living in symbiosis with the cell and stimulating its growth has not been substantiated, and indeed is incompatible with the nature of many tumors, certain parasites are unquestionably very closely associated with the origin of some neoplasms. In some tumors of the lower animals the parasitic process



would appear to tend more often than in man to assume autonomous qualities, nevertheless, animal parasites do figure in certain tumors of man as direct or indirect exciters, and give rise both to benign and malignant neoplasms. In man *Schistosoma haematobium*, *Schistosoma mansoni*, *Schistosoma japonicum*, *Onchocerca volvulus*, and *Onchocerca caecutiens* are the parasites which not infrequently act as the inciting agent in the production of the neoplasms.

Tables I and II enumerate the more important helminths which are concerned in the production of tumors in both man and animals, together with the names of some of the investigators who have particularly described the condition.

TABLE I  
Parasites Associated with Neoplasms in Animals

Parasite	Host	Lesion	Author
<i>Gongylonema neoplasticum</i>	Rat	Carcinoma of stomach	Fibiger Wassink Yokogawa
<i>Taenia crassicolis</i> ( <i>Strobilocercus</i> ) ( <i>Cysticercus fasciolaris</i> ) (Larva) form of <i>Hydatigera taeniaeformis</i> ) ( <i>Redilaenia taeniaeformis</i> )	Rat	Sarcoma of liver	Borrel Bridro Bullock and Curtis
<i>Taenia multilocularis</i>	Dog	("Tumeur echinococcique alveolaire")	Brumpt Mangold
<i>Fasciola hepatica</i>	Cattle Buffalo Sheep, etc.	Adenoma of liver	Brumpt Massia and Moronos
<i>Melorchis conjunctus</i>	Fox	Adenoma of liver	Tyzzer
<i>Hepaticola gastrica</i> ( <i>Trichurinae</i> )	Rat	Carcinoma of stomach	Sambon and Baylis Wassink Beatti Bonne Vogel
<i>Trichosomoides crassicauda</i>	Rat	Papillomata and Carcinoma of bladder	Saul Thomas Löwenstein Wassink
<i>Onchocerca gibsoni</i>	Cattle	Fibrous nodules	Cleland and Johnston Glruth and Sweet Breinl
<i>Spirocerca sanguinolenta</i> <i>Spirocerca arica</i> <i>Spirocerca felineus</i>	Dog Fox Wolf Cat	Fibromatous nodules in esophagus, stomach, lung, and aorta, abdominal cavity, lymph glands	Seurat Hoeppli Hiyeda Faust
<i>Heterakis isolanche</i>	Pheasants	Nodular typhlitis or submucous fibro-sarcoma of caecum	Klee Railliet Galli-Valerio Sambon Wassink Schwartz, etc.
<i>Muspicca borrelli</i>	Mice	Carcinoma of mammary gland	Borrel Haaland Brumpt

TABLE II  
Parasites Associated with Neoplasms in Man

Parasite	Lesion	Author
<i>Schistosoma haematobium</i> (Bilharzia)	Carcinoma of bladder	Goebel Ferguson Kartulis Madden
	Carcinoma of liver	Pirie Mouchet and Fronville
<i>Schistosoma japonicum</i>	Carcinoma of liver	Yamagiwa Kazama
	Carcinoma of caecum and rectum	Miyagawa Kusuma
<i>Schistosoma mansoni</i> (Bilharzia)	Polypi or papillomata of colon	Madden Sinderson and Mills Dolbey and Fahmy Martinez
	Fibroma of appendix	Mouchet and Fronville
	Carcinoma of rectum	Madden
	Carcinoma of caecum	Roman and Burke
<i>Opisthorchis felineus</i>	Carcinoma of liver in fish eaters	Askanaazy
<i>Opisthorchis sinensis</i>	Adenoma and Carcinoma following cirrhosis of liver	Joyeux Watson-Wemyss
<i>Taenia multilocularis</i> ( <i>Echinococcus granulosus</i> )	Adenoma of liver	Jenckel Dévé, etc.
	Carcinoma of liver	
<i>Onchocerca volvulus</i>	Subcutaneous fibromata	Brumpt Fülleborn Blacklock Robles Calderon Sharp Strong
<i>Onchocerca cutcutiens</i>	Subcutaneous fibromata	

Obviously it is not unreasonable to conjecture that under some conditions the irritation caused by certain parasites may lead to tumor formation in different parts of the body. However, the production of such tumors, by the parasites concerned, is not constant, and just why a neoplasm results in some instances and not in others has not been clearly demonstrated.

It has been suggested that the irritant in helminthic neoplasms is specific, some product of the metabolism of the parasite, or that the new growth results from mechanical irritation; while Borrel suggested that the parasite acts as the carrier of a special virus which gives rise to the tumor. Certainly we cannot lose sight in many instances of the influence of the parasite acting as a mechanical irritant in the production of the neoplasm, and often, it is at least the important exciting or preparatory factor. Whether some other factor, such as a filterable virus or (more likely) an abnormal cell metabolism, is not in addition necessary or directly responsible for the tumor production also is not yet entirely clear. Opposed to the supposition that the parasites may produce special growth-inciting secretions, is

the fact that not one species of parasite but different ones belonging to widely different groups of parasites may be concerned in the tumor formation, as is evident from Tables I and II. Sambon pointed out that when several or many individuals of the same species of parasite invade an organ, the liver, for instance (as in the case of *Strobilocercus fasciolaris*) they do not all give rise to neoplasms. One or two only do so, if any; rarely more. In fact, it should be emphasized that the formation of the tumor about the parasite is by no means an inevitable sequel to infestation with it, but that, on the contrary, the development of the neoplasm in the presence of at least some parasites is infrequent. In other instances it is not the parasite itself that produces the neoplasm, but its ova, acting as inert foreign bodies. Moreover, while *Gongylonema* will give rise experimentally to gastric carcinoma in rats, it does not do so in mice. There has been but a single exception reported by Bayon. *Gongylonema pulchrum*, which has been reported from man in at least eight cases, in both Europe and America, by Alessandrini, Ward, Stiles, Ransom, Faust and others, has been found solely about the oral cavity (the epithelium of the lips, floor of the mouth, or tongue). There has been no evidence of the formation of any neoplasm in these cases.<sup>1</sup> The numerous *Gongylonemata* found commonly embedded in the epithelium of the esophagus of cattle and in swine and sheep, also give rise to no neoplasms. Stiles and Baker have shown that when *Gongylonema pulchrum* is introduced into white rats it has given rise to no new growths in the two instances of infection which resulted. Baylis considers that *Gongylonema neoplasticum*, Fibiger and Ditlevsen, 1914, is possibly synonymous with *Gongylonema pulchrum*.

So it is obvious that some other factor in addition to the parasite must be necessary in many instances for the production of the neoplasm. Whether this unknown factor is inherent in the cells of the host, or whether it is sometimes introduced by the parasite itself, is not definitely proved. Perhaps the filterable viruses that give rise to sarcoma in fowls may stimulate cell growth in a somewhat similar manner as the animal parasites, about which neoplasms are formed. Nevertheless, the appearance of neoplasms in connection with the

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<sup>1</sup> In Alessandrini's case there were six worms occupying sinuous sinuses at the base of the tongue. One parasite was taken from a small papule, the size of an acne pustule in the floor of the mouth, on the left side of the tongue.

presence of certain parasites is of such frequent occurrence that we are compelled to recognize that they must play an important part in the production of such blastomata.

Among the animal tumors particularly striking, are the massive sarcomata of the liver of rats which have been so frequently produced and studied recently, especially by Bullock and Curtis. Such tumors have been produced in rats by feeding the animals faeces of cats containing the embryonated-ova (*Cysticercus fasciolaris*) of *Taenia crassicolis*. The shells of the ova are dissolved in the digestive juice of the rat's stomach and the freed larvae pass through the walls of the intestinal blood-vessels into the portal circulation and are carried to the liver where they lodge in the capillaries and eventually give rise to the neoplasms. Histologically these tumors are true sarcomata, either of the round-cell or spindle-cell form. During the years 1920 to 1930 Bullock and Curtis have produced *Cysticercus* sarcomata in over 2,450 rats. Their extensive studies demonstrate very conclusively the association of *Taenia crassicolis* with the production of the tumors.

In a study of 1,400 *cysticercus* tumors in rats, Bullock and Curtis found that all were of mesothelial origin and all except one were malignant. Two of the neoplasms contained hyaline cartilage and two contained both cartilage and osteoid tissue or bone. Of these four tumors, one was an osteoid chondroma, one a chondrosarcoma, one an osteo-chondrosarcoma, and the other a mixed-cell sarcoma containing islands of cartilage. Still later they encountered another *Cysticercus* chondroma or chondrosarcoma, and finally a carcino-osteo-chondrosarcoma of the rat liver. In addition, they observed that two rats developed benign cystadenomata which apparently originated in isolated bile ducts in the walls of *Cysticercus* cysts. These two adenomata and the one carcino-osteo-chondrosarcoma were the only epithelial growths which had arisen in the walls of the parasitic cysts among more than 2,100 rats in which *Cysticercus* sarcomata were produced. They suggest two explanations for the failure of the epithelium of the liver to participate more frequently in the neoplastic process inaugurated by the *Cysticercus*: (1) that the liver cells and bile ducts may be more or less protected from the irritant elaborated by the parasite by the fibrous cyst wall which encloses the larva. They point out that the outer parts of the wall of many cysts

contain bile ducts and isolated liver cells or groups of cells, but these are more or less remote from the cyst cavity. As the sarcomatous process progresses the barrier between liver and larva is correspondingly strengthened by the increased amount of tissue separating them, whether the sarcomata arises from the cells lining the cyst or the deeper lying cells in the cyst wall. The fact that some sarcomata do originate in the outer part of the cyst wall suggests that the irritant sometimes comes in contact with the outlying connective tissue cells of the wall and probably with the epithelial cells included therein; (2) that the hepatic cells and bile duct epithelium may be more or less resistant to the proliferative action of the parasite, or these cells possess little or no predisposition to neoplastic changes from any form of irritation. Yet the liver cells are not irresponsive to stimulation by the parasite in its early stage of development, but participate actively in the proliferative process engendered by this organism. At this time the liver cells are exposed to the direct action of the parasite.

They conclude that the infrequency of spontaneous epithelial tumors of the liver of rats speaks for the relative insusceptibility of the hepatic epithelium to neoplastic changes. In man, on the contrary, the liver cells are highly susceptible to the irritant of another type of helminth as is shown by the great frequency of primary liver carcinoma among those infected. Bullock and Curtis, however, add that although it is doubtful if either of these explanations suffices to account for the paucity of *Cysticereus* epithelial tumors, it is not improbable that both the indisposition of the hepatic epithelium to neoplastic proliferation and the protection afforded the epithelium of the cyst wall are important factors.

Beatti in Buenos Aires, Sambon and Baylis in Italy, and Wassink in Holland have all encountered carcinoma of the stomach in rats found naturally infected with *Hepaticola gastrica* or *Hepaticola hepatica*. In the natural infections of rats observed by Beatti, the parasite is designated as *Hepaticola hepatica*. Baylis, on the ground of differences in the eggs, regarded the stomach inhabiting, *Hepaticola gastrica* as specifically distinct from the liver inhabiting, *Hepaticola hepatica*. Sambon believes that Beatti's observations concerned *Hepaticola gastrica*. Uyeyama in Tokyo has found in four white rats, in connection with epithelial new growths of the stomach, in-

fection with similar nematodes which, however, he describes as a new species under the name of *Hepaticola muris*. Vogel has recently extended these observations on the production of gastric carcinoma in rats with *Hepaticola gastrica*. By feeding the mature eggs of this parasite to four young black-white rats, in two of these after about three months there originated typical epithelial carcinoma of the cardia of the stomach. Vogel has given a careful description of the pathologic histologic changes in these tumors together with illustrations of the same. *Hepaticola hepatica*, a very closely allied species living particularly in the liver of rats and mice in various parts of the world, does not apparently give rise to any neoplasm. The pathologic process in the liver consists in the formation of fibrous connective tissue around the deposits of ova, and in light infections only a localized area is involved, while in heavy infections there may be a generalized cirrhosis of the liver. Ten cases of human infection have so far been recognized, one by MacArthur and nine by Faust. Faust has merely recorded the presence of the ova in his cases. In MacArthur's report upon material furnished by Dive, the symptoms of the patient were said to resemble pyemia, and the postmortem examination revealed a suppurative condition of the liver with spongy areas in which the microscope revealed the presence of large masses of the ova of *Hepaticola hepatica*.

Recently Brumpt has made a critical study of the rôle Bilharzia (*Schistosoma*) plays in the production of human carcinoma, and Sorour has presented statistics proving the association of Bilharzia with malignant tumors. Brumpt, in reporting upon an instance of vesicular carcinoma in Cairo, points out that the statistical studies (demonstrating that the association of bilharziosis and of cancer of the bladder is from two to eleven times more frequent than pure cancer of the bladder), permit us to affirm the etiologic rôle of the ova of Bilharzia to the production of cancer of the bladder. He, however, feels that just what is the rôle of Bilharzia in the formation of primary cancer of the liver and of the rectum, remains still to be demonstrated conclusively. However, Sorour points out that it is an actually established fact that malignant tumors are frequently associated with Bilharzia in the following tissues noted in order of their frequency: bladder, cirrhotic liver, rectum, peritoneum, and skin in the inguinal region. He has collected 413 cases of bil-

harziosis of the bladder, of which 393 were in men and twenty in women. Among the 393 men there were: seventy-eight cases of cancer of the bladder; four of sarcoma of the bladder; three of bilharzial endothelioma of the peritoneum; four of bilharzial cancer of the rectum; one of bilharzial cancer of the cecum; and one of bilharzial epithelioma of the skin in the inguinal region. Among the twenty women there were two cases of cancer of the bladder. His statistics further show that bilharzial carcinoma of the bladder appears in the first period of life, from fifteen to twenty years of age, but that it becomes augmented in frequency as age progresses. With reference to primary cancer of the liver and its association with bilharziosis, he points out that this tumor occurs as a complication of the cirrhosis of the liver which is caused without doubt, principally in Egypt, by Bilharzia. In his statistical study of 342 cases of cirrhosis of the liver with autopsies which covered the same period, during which the cases of bilharziosis of the bladder were observed, there were 225 cases showing diffuse bilharzial cirrhosis. The incidence of tumors of the liver in these cases is as follows: fifteen cases of primary cancer of the liver (about 6.6 per 100); one case of multiple adenoma of the liver; three carcinomata of the gall-bladder with secondary carcinoma of the liver; two carcinomata of the pancreas with secondary carcinoma of the liver; two secondary carcinoma of the liver; one sarcoma of the gall-bladder; one case with adenomatous nodules in the liver. From his table of statistics it may be seen that the primary cancer presents itself in diffuse bilharzial cirrhosis from the age of twenty to twenty-five years, and thence onward in the different periods of life up to seventy to eighty years. He emphasizes that the primary carcinoma of the liver occurs only where there is diffuse bilharzial cirrhosis in which the eggs of the Bilharzia are deposited in the parenchyma and consequently find themselves in close relation with the liver cells. In eighty-nine cases of periportal cirrhosis where the eggs were deposited in the capsule of Glisson and did not come into contact with the cells of the liver, no case of carcinoma was noted.

*Schistosoma japonicum*, *Opisthorchis felineus* and *Opisthorchis sinensis* likewise may all give rise in cases of severe infection and of long standing to biliary cirrhosis, and several observers regard such a cirrhosis as a pre-cancerous condition. Yamagiwa, Watanabe,

tissues. Nor has such a malignant condition in association with this parasite been observed in animals or produced experimentally in them. He inclines to the belief that it is more probable that the parasite acts as an irritating foreign body and that in the chronic inflammatory reaction which occurs the *Echinococcus* cyst may in some instances become an irritative precancerous factor.

Fibromatous nodules in association with *Spirocerca* have been reported in animals, particularly in the esophagus, stomach, lung and aorta, and sometimes in the abdominal cavity and lymph-glands. The histology of these lesions has recently been studied by Hoeppli and by Hiyeda and Faust. Hoeppli, in the study of a hazel-nut-sized tumor in the stomach wall of a dog, found that the mucous membrane was preserved over the greater part of the tumor with the exception of its summit. Here there was an opening in which two nematodes (*Spirocerca sanguinolenta*) were enclosed. The submucosa was particularly the seat of the pathologic changes, in which there was marked proliferation of the connective-tissue fibers. Within the fibrous tumors the parasites were enclosed in irregular cavities. Sometimes between the cyst wall and the parasite within there were observed necrotic zones in which were situated degenerating polymorphonuclear leukocytes. The proliferated connective tissue was rich in blood-vessels. In the more central portions of the connective tissue he found numerous mononuclear cells with eccentric deeply staining nuclei. Eosinophils were not numerous. Hiyeda and Faust have studied particularly the aortic lesions in dogs due to *Spirocerca sanguinolenta* which they find are of two types: (1) nodular and (2) aneurysmal in character. In the early stages hemorrhage and purulent inflammation result. The inflammation seems to be due to by-products of the worms. Following the purulent inflammatory condition in the aortic wall, there is a destruction of muscle and elastic elements and a replacement of these with growths of dense fibrotic and fibroblastic tissue.

The submucous nodular tumors produced by several species of *Oesophagostomum* in both man and animals are also particularly the result of an inflammatory process. Cysts first develop around the larvae. In the cyst wall—there is an inner zone of lymphocytes and polymorphonuclear leukocytes surrounded by fibrous connective tissue lying in the submucosa or muscularis. The developing worms



finally cause a rupture of the cysts which may result in a hemorrhage from the adjacent blood-vessels. The formation of fibrous connective tissue in the vicinity enclosing the parasite within the nodule eventually often occurs. In the same category may be classified the nodular tumors produced by *Gnathstoma spinigerum*. This parasite was first reported by Owen in nodules of the stomach of the tiger. The writer recently encountered an instance of infection with this parasite in a leopard which was shot in Africa. The small intestine of the animal contained numerous nodular tumors measuring from about one to three centimeters in diameter lying in the submucosa; the mucosa and adjacent tissues being pushed upward into the lumen of the intestine. Sections of these nodules revealed the presence of encysted parasites. A histologic study of these nodules in the submucosa showed that there was a very dense cellular infiltration, particularly of lymphocytes and plasma cells. In other portions of the tissue there were small areas of necrosis with a deposition of fibrin and many degenerating polymorphonuclear leukocytes. Outside the more acute areas of infiltration the tissue was more fibrous in character with small islands of infiltrating cells. Some eight cases of infection with this parasite have also been observed in man. Deuntzer apparently observed the first case in a young Siamese woman who suffered from a small tumor of the breast which had developed in the course of a few days. In this as well as in the other cases the parasite gave rise to a fairly acute inflammatory reaction, and no true neoplasm resulted.

*Heterakis isolanche* is a parasite limited to certain species of pheasants and responsible for a fatal nodular disease of the caecum first discovered by Klee in Germany in 1891 and by Railliet in France the following year. It has since been reported from Italy by Galli-Valerio in 1896, from England by Sambon in 1908, from Holland by Wassink in 1916, and from the United States and Canada by Schwartz in 1924. The neoplasm is usually confined to the caecum but may occasionally occur in the large or small intestine. It lies under the mucosa between it and the muscular coats but the growth may invade the muscular coat and even reach the serosa. Letulle and Marotel, and Lucet and Henry have described the neoplastic spindle-cell texture of the nodule produced by this nematode. The

man, had the opportunity of studying a small cystic tumor produced by *Loa loa*. The tumor measured about five centimeters in diameter and was situated on the right arm about six centimeters above the elbow and lying along the inner aspect of the biceps muscles in the subcutaneous tissue. It was freely movable, soft and cyst-like. The examination of the peripheral blood from the ear of this patient showed long, thin, filarial embryos with a sheath which from the examination of stained preparations suggested *Microfilariae loa*. Microscopic preparations made from the inner wall of the tumor showed a number of red-blood corpuscles and a few similar microfilariae. The tumor was removed and fixed in formalin. It proved to be a thin-walled cyst containing straw-colored fluid and a single parasite about five centimeters in length lying free in the fluid. There is no evidence of inflammatory change in the cyst wall of the tumor and there is no cellular infiltration of the surrounding connective tissue. The cyst probably represents a dilatation of a gland-like cavity. It appears as though the fibers of the surrounding tissue had gradually been pressed apart by the movements of the parasite and the slowly accumulating fluid. In the surrounding tissues a few millimeters outside the cyst wall, there are wavy bands of areolar connective tissue with a few red-blood cells and leukocytes lying within the interstices. It seems probable that the parasite originally developed to its adult size within a lymphatic vessel whose walls gradually became occluded; however, it is impossible from the structure of the cyst wall to definitely assert that such was the case.

Rodhain has described in an antelope keloidal nodules in the skin from one to five centimeters in size produced by a new species of filaria (*Filaria pertenuis*).

Parasites of the genus *Onchocerca* are particularly concerned in the production of subcutaneous fibromata. In Australian cattle *Onchocerca gibsoni* is the species concerned, while in man *Onchocerca volvulus* in Africa, and *Onchocerca caecutiens* in Guatemala and parts of Mexico, give rise to the tumors. Recently, Cameron has described a species of *Onchocerca* found in subcutaneous nodules in an ox in West Africa. He says that morphologically there does not appear to be any valid difference between this species and *Onchocerca volvulus* and *Onchocerca gibsoni*. The measurements are approxi-

FIG. 1.



FIG. 2.



Onchocecal tumors in Africa.

FIG. 3.



FIG. 4.

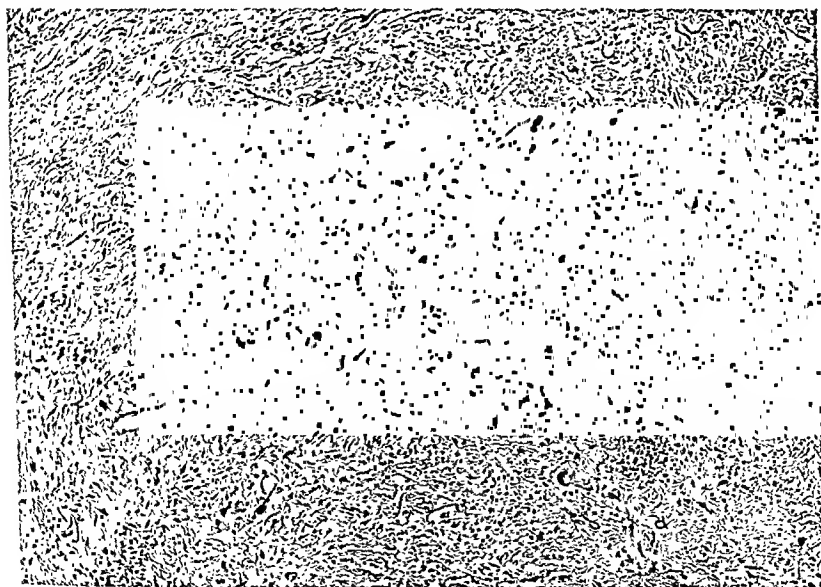


FIG. 5.



Photomicrograph of larval form of *Onchocerca volvulus*. Moist film preparation made from cut section of tumor.

FIG. 6.



Photomicrograph of section of fibromata, showing numerous larval forms of *Onchocerca volvulus*.

FIG. 7.



Onchocercal tumor, Guatemala.

FIG. 8.



Camera lucida drawing of section of pericorneal conjunctiva with *Onchocerca cecutiens* microfilariae.

mately the same. There were slight differences only in the arrangement and the number of the papillae in the male. Hoeppli has observed tumors in the vaginal wall of a dolphin in which a species (undetermined) of *Onchocerca* was encountered. Breinl has given an excellent account of the nodules as they occur in cattle in Australia, while the human tumors have recently been studied in Africa, particularly by Brumpt, Fülleborn, Blacklock and the writer, in Guatemala by Robles and Calderon and the writer, and in Mexico by Ochoterena and Arroyo. (Figs. 1-8.)

Infection with *Onchocerca volvulus* is very common in parts of Africa, particularly in the central and western portions. In some localities as many as 10 per cent. of the natives are affected. The tumors usually measure from one to six centimeters in diameter and are commonly found about the chest wall, particularly in the lateral regions, in the intercostal spaces and occasionally on the dorsum. They also occur in the neighborhood of the joints and in the axilla. As a rule they are firm and grayish-white at the periphery, but there are often soft areas in the more central portions, particularly in those areas which have a yellowish or orange color. It is in these soft areas or cavities that the adult parasites are particularly found together with enormous numbers of the microfilariae. The tumor is frequently surrounded by a capsule. Histologic examination of the different tumors collected in various localities in Africa show that they are all fibromata. In the center, sections of the adult parasites are commonly found usually imbedded in the connective-tissue stroma. Immediately about the parasites there is often some evidence of irritation caused by the parasite itself. A few polymorphonuclear leukocytes are scattered about with small round cells, occasionally plasma cells, and eosinophils. Outside of these areas the tumor is composed largely of fibrous connective tissue. Here the fibroblasts are few in number and the fibroglia fibrils are not abundant. The tumor is composed particularly of collagen fibers forming wavy bundles. In none of the tumors do the cells show marked evidence of mitotic division, nor are numerous giant cells present, so there is no evidence that the neoplasms are formed very rapidly. However, Hoeppli who studied one onchocercal tumor histologically, found numerous giant cells, and in sev-

ent in the sections of the epidermis or conjunctiva are actively motile and measure from 150 to 250  $\mu$ , rarely from 285 to 300  $\mu$  in length and from 6 to 6  $\mu$  in width. They are not found naturally in the blood. When, as might rarely happen, one has been seen in a preparation of the blood, it has evidently come from a lymphatic vessel punctured in obtaining the specimen. If a thin section of the epidermis of the face or neck of an infected individual is made (preferably with a safety razor blade), without causing any flow of blood, and is examined fresh in a drop of normal saline solution, one or two motile microfilariae, up to four to eight are usually found; occasionally as many as fifty are observed.

Doctor Bequaert and the writer, working in Guatemala, have been able to demonstrate that three species of *Eusimulium* flies are concerned in the transmission of the disease (*Eusimulium avidum*, *Eusimulium ochraceum*, and *Eusimulium mooseri*). All stages of development of *Onchocerca caecutiens* have been repeatedly observed in these flies, and the development has been traced from the time the fly bites the infected individual and thus ingests the microfilariae from his skin, on through their passage and development in the thoracic muscles, head and proboscis.

The conditions under which Onchocerciasis occurs in Guatemala are widely different from those under which it prevails in Africa. Recent investigations in Guatemala have disclosed the fact that conditions are such in that country, that by the inauguration of a proper public health campaign, the disease there might be eradicated entirely. The affection in Guatemala is confined to rather sharply circumscribed areas, especially about coffee plantations with an altitude of from 600 to 1400 meters. In such localities from one-third to two-thirds of the inhabitants are affected with onchocercal tumors. Certain public health procedures are of importance and must be carefully carried out for the eradication of this disease. As the breeding-places of the *Eusimulium* concerned in its transmission are so widely distributed in practically every swiftly flowing stream of water in the neighborhood, the eradication of these flies in such coffee districts is entirely impracticable.

Every severely infected case constitutes a focus of infection. Many individuals are so badly infected that every *Eusimulium* fly which bites them is likely to ingest a hundred or more microfilariae,



while in a mildly infected case a fly may not take up more than one or two microfilariae. Public health procedures should include inspection of the inhabitants in the endemic districts and the diagnosis of the cases with filarial tumors with prompt removal of the fibroid growths. The operations are simple and easily performed under local novocain anesthesia. However, the microfilariae do not always disappear immediately following the operation, but sometimes persist for a considerable time thereafter.

In order to rid the patient of the microfilariae which may persist after the removal of the tumors, experiments were performed to discover a satisfactory filaricidal substance. It was found that *in vitro* plasmoquinin in dilutions up to 1 to 10,000 effectively destroys the microfilariae. Quinine in a dilution of 1 to 5,000 also produces somewhat similar results. The results obtained with these substances were so encouraging that they give hope for the destruction of the microfilariae in the tissues of man, if prolonged treatment with sufficiently large doses can be employed. It is not at all likely that the adult parasites so well protected by their structure and located in the center of the tumors will be destroyed or even unfavorably influenced by such treatment, but plasmoquinin is certainly inimicable to the existence of the microfilariae, and in a few instances they have at least temporarily disappeared from the skin following a short course of treatment with relatively small doses of this drug. However, about a month after discontinuing the plasmoquinin, in several such cases microfilariae were again found in the skin, suggesting either that they had not been entirely destroyed or, what is perhaps even more probable, that these patients still harbored adult parasites that were producing additional larvae. In cases in which after removal of the tumors (together with the adults contained in them), the microfilariae persist in the skin and do not disappear under treatment with plasmoquinin, a careful search should be made for small nodules beneath the skin. In some such instances, with persistence of the microfilariae, it is clear that adult parasites may still be present, concealed somewhere in the lymphatics, giving rise to large numbers of new larvae. While in Guatemala we found few individuals with *Microfilaria caecutiens* in the skin with no visible tumors, nevertheless such cases were observed in at least 4 to 5 per cent. of the inhabitants examined. This condition is

again different from what is found in Africa where the percentage of infection with *Onchocerca volvulus* with no visible tumors is very much higher. In Guatemala periodic microscopic examinations should be made in each individual after operation to detect the number of microfilariae which persist. If large numbers of microfilariae are still present, the individual should be regarded as a dangerous carrier and be isolated until the parasites diminish or disappear through treatment.<sup>1</sup>

While then in the case of onchocercal tumors the results obtained by surgical intervention and treatment are usually satisfactory, in the case of the other human tumors (carcinoma of the bladder, liver, and intestine) associated with the parasites, there is little hope of the eradication and cure of the condition by treatment.

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<sup>1</sup> While this article was in press a report by Torroella (*Medicina, Revista Mexicana*, Sept. 10, 1931, vol. xi, p. 761) has appeared, in which the value of plasmochin in onchocerciasis is confirmed, and ocular cases successfully treated by injections.

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were repeatedly cultivated from the stools by a special concentration method. The patient felt well while in bed but she was conscious at times of afternoon or evening fever, especially during the two weeks preceding catamenia, when the evening temperature was often 100 to 100.4° F. (rectal). *Brucella* were not obtained by intra-uterine culture or from the menstrual fluid. Because of recurrent twinges of pain in the lower right quadrant of the abdomen, the patient herself suggested operation for chronic appendicitis as she was in excellent physical condition for laparotomy. At operation Dr. J. Deryl Hart found a most surprising appearance. The outer end of the right tube was slightly indurated and on section showed lesions suggestive of tuberculosis. Two large acid-fast bacilli were found in the examination of several sections. A guinea-pig inoculated with this material developed tuberculosis and cultures yielded *brucella*. From a few small cysts on the right ovary and from enlarged glands in the broad ligament, *brucella* were obtained in pure culture. The appendix was slightly enlarged and fibrous, and the ileocecal glands were much enlarged. These tissues likewise yielded *brucella*. On the meso-appendix and the mesentery, over the serous coats of the intestines, and on the peritoneum were many discrete white papules presenting a picture of tuberculous peritonitis. The white papules were softer than tubercles. The histologic picture resembled tubercles with giant cells and lymphoid infiltration but there was less fibrous tissue than in the ordinary tubercle. No tubercle bacilli were seen and none was recovered by guinea-pig inoculation, but a pure culture of *brucella* was obtained from them and from the cystic right ovary.

The patient recovered quickly from the operation and was discharged from the hospital, but continued treatment for one year by rest and heliotherapy. She has been examined frequently for the past two years, and her temperature recorded twice daily during this time. For about one year there was a slight fever during the premenstrual period but this together with the attending symptoms gradually subsided, and she has resumed her work as a teacher of Spanish.

*Brucella* does stimulate the production and provocation of agglutinins which are usually detectable in the blood during the second week of the disease and sometimes increase to a very high titer. In the first case of human *brucella* infection not associated with goats,

reported by Keefer in 1924 from our laboratory, the patient's serum agglutinated the homologous strain in a dilution of 1:20,000. But as in typhoid fever, there seems to be no relation between recovery from the infection and the agglutinin titer. In both of these infections there may be a pre-agglutinoid zone of considerable spread. In Keefer's case there was no agglutination until a dilution greater than 1:1200 was reached, although there was complete agglutination from that point to 1:20,000. The fact that agglutinins, although present in high concentration, cannot act in the serum unless it is diluted may be one explanation of the lack of correlation between agglutinin content of the blood and the course of the disease in both brucella and typhosis infection.

The agglutinins usually persist in the blood during the acute general infection but gradually disappear, although the infection may localize and persist for years. Thus a local infection of brucella may be present and give rise to incapacitating symptoms without any agglutination reaction in the blood. This fact is of especial import in diagnosis. Two cases will illustrate this point.

A Virginia merchant,<sup>2</sup> aged thirty-four, presented a history quite characteristic of intermittent hydrarthrosis of seven months' duration. As one knee would swell to attain a maximum in three and a half days, the swelling in the other knee would recede to normal during the same period. Plotting of the circumferences of both knees daily over a period of months yielded a symmetrical double sine curve. Brucella was obtained from blood cultures and twice from the material obtained by puncture of each knee-joint, but the agglutination reaction with the homologous and other strains remained completely negative throughout the several months of observation.

The other case in which there was localization of brucella with persistence of symptoms without the presence of blood agglutinins at the time at which she came under observation was that of a woman\* of forty-eight who contracted the infection while working with these organisms in the laboratory seven years before entry into the hospital. She had had symptoms but did not suspect brucella infection until her own serum, used as a control in some experiments, showed positive agglutination. The organism was recovered from blood cul-

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\* This case has not been reported in detail. It will be reported by Dr. George P. Berry.

ture during a febrile attack. There were two marked waves of fever and a period of improvement, but she never regained her health and became a patient in several hospitals. In the spring of 1928 she came into the Johns Hopkins Hospital for observation. There was a slight fever but the blood count was normal. She complained of insomnia, sweating of the upper part of the body and fatigability with nervousness and lancinating and dull pains in the left thigh. Blood cultures and agglutination reactions were consistently negative. There were no abnormalities found on physical examination except an asymmetrical enlargement of the uterus. At operation for hysterectomy Dr. Richard W. Te Linde found several small hemorrhagic cysts in the left ovary, which otherwise seemed to be normal. From the fluid in these cysts a pure culture of brucella was obtained. The patient gradually improved and returned to work but began again in January, 1931, to have a return of symptoms with pains in her right shoulder and humerus. She entered the Duke Hospital June 1, 1931. There were no abnormalities found on physical examination and no abnormalities found by X-ray examination of the gall-bladder. However, brucella was grown twice from the bile obtained by duodenal drainage. Because of previous experience in gall-bladder infection with brucella, operation was advised. Dr. J. Deryl Hart removed the thickened gall-bladder and performed a gastro-enterostomy on account of an unsuspected peptic ulcer discovered at operation. Brucella was recovered from the bile and the posterior wall of the gall-bladder but not from the surface of the ulcer. The patient remains in the hospital because of a mild cystitis which is not improving.

Another instance of gall-bladder infection was discovered in the autumn of 1929. The patient was a physician of forty-five who had an acute attack of fever of three weeks' duration with gastro-intestinal symptoms, weakness, fatigability and sweating, persisting for the ensuing three months. The serum agglutination was positive for brucella and the organisms were obtained from the stools repeatedly and from the bile, withdrawn by duodenal drainage. X-ray examination of the gall-bladder showed no abnormalities. After cholecystectomy by Dr. J. M. T. Finney, who found a much thickened posterior wall adherent to the liver, the patient recovered completely and has remained well for two years.

Brucella has been found by other observers in the tonsils, on the



endocardium, and in the spinal fluid. Apparently all tissues may be invaded by this organism and remain infected over long periods.

In animals also the infection has been found widely distributed. The predilection of the organism for the genital tract in cows, and the occurrence of the organism in cows' and goats' milk are well known. In male guinea-pigs inoculated subcutaneously or by scarification, the organism generally localizes in the testicles and has been found in all tissues, even in the bone-marrow.

One of our patients<sup>3</sup> apparently received his infection from handling embryologic material obtained from swine, and another<sup>4</sup> became ill while employed as a stripper of hog intestines. Both strains of brucella apparently belonged to the bovine type of *B. abortus*.

#### DISCUSSION

In both man and animals there is evidence that some strains of brucella are active invaders of all tissues. Meyer has shown this to be true in experimental studies in monkeys. The organisms quickly gain entrance to the blood-stream and may be present there over long periods. With such wide distribution all tissues become repeatedly infected. Evidence has been adduced in this paper to suggest that phagocytosis by pus-cells and defense by agglutination are probably not sufficiently operative to destroy the invader. There remain to be studied the reaction of the reticulo-endothelial cells, individual cell resistance to invasion, and the bacteriostatic and bactericidal powers of body fluids. With the evidence at hand localization in any tissue is not surprising, and it is probable that, as broader experience is acquired, localization in other sites in man will be found, as has already been shown to be true in the lower order. In the present state of our knowledge the only logical explanation of localization is chance distribution.

#### SUMMARY

Cases are recalled in which brucella was found localized in the fallopian tube (associated with the tubercle bacillus), in the glands of the meso-appendix, in the appendix, in the gall-bladder contents and walls, in benign cysts of the ovaries, and distributed over the serous surfaces of the intestines simulating tuberculous peritonitis, and in the joint fluid from a case of intermittent hydrarthrosis. The

histories suggested that the organisms had been present in these sites for long periods.

Cases have been described by others in which there has been localization in the tonsil, on the endocardium, and in the spinal fluid. In animals the organism has been found in all tissues.

There is no evidence that the organisms are destroyed by the agencies of phagocytosis by pus-cells or that agglutination plays any rôle. At present the only explanation of localization is chance distribution.

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- <sup>4</sup>Reported by Leavell, Poston and Amoss.

# CHRONIC URTICARIA AND ANGIONEUROTIC EDEMA

By LOUIS M. WARFIELD, A.B., M.D.

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SINCE the discovery of the allergic skin response to various protein substances an enormous amount of work has been done upon the diseases associated with sensitiveness to proteins. It was inevitable that some enthusiastic workers would swing the pendulum too far, so that patients were subjected to dozens of skin tests. As time has gone on and a saner view has prevailed it is found that relatively few protein substances<sup>1</sup> are responsible for the manifestations of allergy. These manifestations comprise a group of diseases seemingly unrelated but in reality very closely related. Among them are certain types of asthma, hay fever, eczema, dermatitis (some forms), urticaria and angioneurotic edema.

Edema has been the subject of intensive study during the past few years. It would be of no value and lead us far afield to discuss edema in general. Our interest is in the local edema causing urticaria and angioneurotic edema.

In general edema may be classified into (1) inflammatory and (2) mechanical. The latter is probably the result of capillary ultrafiltration and differences in osmotic pressure. The edema fluid is low in protein. The former depends to great extent on capillary injury and capillary permeability. The edema fluid is rich in protein. Certain ions of the metals Ca, K, and Na have been shown to have a marked influence on capillary permeability, the Ca ion decreasing permeability and causing contraction of the capillaries, the K and Na ions increasing permeability and causing dilatation of the capillaries. In the normal organism there is a nicely adjusted balance between these ions so that capillary diffusibility occurs between the blood and tissues without the formation of edema.

Even before it was known that capillary permeability was dependent upon the prevalence of more or less of the Ca, K, and Na ions, calcium salts had been given empirically in cases of urticaria and angioneurotic edema with good results now and then. The cause

of the irregularity in results was not understood until workers began to determine the calcium in the circulating blood. It was then found that patients with low calcium values in the blood serum were the ones who, for the most part, responded best to calcium therapy.

However, to raise the level of calcium in the blood serum by ingestion of calcium salts or even intravenous administration was not always possible. At best, the circulating calcium may not represent the available calcium. As has been pointed out there are the diffusible and non-diffusible calcium fractions in blood serum.<sup>2</sup> Further, one must take account of the phosphorus as well as of the calcium as the two substances have a close relationship. This is particularly true where bone formation is concerned. The phosphorus value of the serum does not appear to be as important in the urticaria-angioneurotic edema group of disturbances.

A number of investigators have laid down normal values for the calcium in blood serum. It is now generally agreed that the number of milligrams of total serum calcium per 100 cc. varies within small limits, from 9 to 11 mgs. (Cantarow). These figures are so constant that one may say definitely that any values below or above are outside the normal limits.

Up to 1925 no one was sure that he could increase the serum calcium by oral or intravenous administration. Collip in 1925 succeeded in extracting the active principle of the parathyroid glands and proved that by the injection of the extract the serum calcium could be raised. This discovery put into the hands of physicians a specific substance which increased serum calcium without any shadow of doubt.

Previously parathyroid extract (dried) in tablet form had been used,<sup>3</sup> and results had been claimed in the treatment of urticaria and angioneurotic edema. However, it is difficult to see that any specific influence upon serum-calcium values could have been exerted as it is known that parathyroid extract given orally is devoid of specific action.

Since calcium has been shown to decrease capillary permeability and since the serum-calcium values are so constant in health, one might reasonably suppose that urticaria and angioneurotic edema were local manifestations in some peculiarly susceptible areas of sudden increased permeability and that the calcium of the blood

should be found decreased. This was the supposition proved to be correct in the case here reported. However, when one consults the literature one finds a most confusing state of affairs. Cantarow,<sup>4</sup> after noting results obtained by various investigators, says, "It must be concluded that the bulk of evidence points to the fact that in most patients with some manifestation of hypersensitiveness or allergy the serum calcium is within normal limits."

Cantarow<sup>5</sup> and his co-workers found essentially the same serum-calcium values as others found but noted (and this seems to be an important point) that the proportion of diffusible to non-diffusible fractions was decidedly changed in that the non-diffusible fraction was always decreased. In the only case of angioneurotic edema this decrease amounted to 100 per cent. with a total serum calcium of 8.2 Mgs., certainly a much-reduced value. Cantarow says, "These findings appear to be indicative of a state of increased *in vivo* calcium diffusibility in atopic disorders." He finds it difficult to reconcile increased diffusible calcium with increased capillary permeability, the evident state of allergic disorders, when calcium decreases cell permeability. "The obvious explanation is, that capillary permeability being increased, more calcium is allowed to pass into the tissue spaces and cerebrospinal fluid, the diffused calcium being increased with no alteration in the diffusibility of calcium as it exists in the plasma."<sup>6</sup>

The diffusible calcium (measured by the calcium in the spinal fluid) and the non-diffusible calcium, that is bound in some way to the plasma proteins, may vary together or independently. Parathyroid hormone raises the level of both fractions but has slightly more elevating effect upon the non-diffusible.

If it were possible to measure easily the two fractions it would enable us to receive reports from various sources which would help to settle the question as to whether calcium partition is disturbed in allergic conditions, and whether any therapeutic measure which definitely raised the level to normal again would have the effect of curing the allergic manifestations.

Unfortunately there is as yet no simple method so that we have to assume that in cases where the serum calcium is diminished, the non-diffusible fraction is more decreased than the diffusible.

From the practical standpoint, the administration of the para-

thyroid hormone plus a calcium salt orally would seem rational therapeutics provided the serum calcium were decreased. It might even be of value when the serum calcium is normal as there are factors in calcium transportation, absorption and elimination which are not fully understood. Normal serum calcium may then mean some faulty distribution which is remedied by specific therapy. Cantarow and Gordon<sup>7</sup> say, "It would appear that parathyroid extract while it may not increase much the values for serum calcium, yet seems to increase the available circulating calcium."

Calcium salts have been employed extensively for some years in the treatment of allergic manifestations. Brown has given parathyroid extract by mouth<sup>1</sup> in small doses combined with calcium salts and has claimed some brilliant results. Cornblut<sup>8</sup> has used parathormone plus calcium salts. He reports good results in the majority of twenty-one cases. He says the combination is better than the hormone alone. O'Leary<sup>9</sup> has seen results from calcium salts alone but has had more consistent results with a combination of thyroid, parathyroid and calcium lactate.

In spite therefore of the fact that the serum calcium is found to be normal in most cases of urticaria, the increase of serum calcium brought about by injection of the parathyroid hormone often produces clinical improvement. Should the serum calcium be low then the definite indication for parathyroid hormone would seem to be present.

The following case illustrates some of the points discussed above.

Mrs. H. L. K. was referred to me September 25, 1930, with the complaint that she had hives inside and outside, suddenly her lips, eyes, or tongue would swell. Practically every day she had hives over the body accompanied by the usual symptoms. Often there would be abdominal cramps with occasional diarrhea. She was much underweight and felt exhausted all the time. There were no allergic diseases in her parents or siblings. She had the usual children's diseases without complications, plus typhoid fever. She had two attacks of pneumonia. Menses began at sixteen years old. Up to twenty years they were irregular. Then they became regular and have been so ever since. She has one child two and one-half years old. The labor was normal. Her tonsils were removed last year as a therapeutic measure on account of urticaria. Several teeth which were devitalized were extracted. Following these operations she felt better for a short while. Her appetite is good, the bowels slightly constipated.

Her urticaria started about eighteen months ago. At first the eruption was not severe but gradually it became so bad that hardly a day passed without an outbreak. Her hands and feet swelled and itched. The lips and eyes swelled

towards evening usually becoming normal by morning. Recently the swelling has lasted more than one day. She thinks that the trouble is worse just before menstruation. She had been under the care of several physicians. Many skin tests had been done with various protein extracts. She reacted to almost every one. A basal metabolic rate was minus 33 per cent. The urine, blood and stomach contents were normal. She had had calcium, and various food substances had been omitted from her diet. She had had heat and cold and non-specific protein fever. None of these measures helped her. Physical examination was quite negative except for the eruption of urticarial wheals scattered over the whole body with swelling of the hands and feet. The routine laboratory tests were quite normal. The gastro-intestinal tract was normal. She had been taking some thyroid extract for some time before she consulted me. Her basal metabolic rate was plus 4 per cent., a normal figure.

The patient was most coöperative, willing to try anything. She had lost ten pounds and felt weak and exhausted all the time. For a while she made no improvement. Then the serum calcium and phosphorus were estimated and found to be 8.51 Mgs. and 1.51 Mgs. per 100 cc. respectively. It was most difficult to enter her vein. The blood vessels seemed to be unusually small. She was then given 15 units of parathormone daily and 90 grains of calcium lactate. After three doses she was nauseated but there was definite improvement in the urticaria and edema. The serum calcium was then 10.9 Mgs. and phosphorus 2.07 Mgs. Curiously enough she had a mild tetany attack (Trousseau's sign) when the tourniquet was put on the upper arm. There was also a violent outbreak of urticaria and edema. The vessels were in such spasm that it was with the greatest difficulty that blood was obtained for the tests. The parathormone was gradually reduced and by December 4th she was eating everything, had gained eight pounds and only occasionally, when tired, did urticaria and edema appear.

TABLE I  
*Blood Calcium and Phosphorus*  
*Mgs. per 100 cc.*

Date	Ca	P	Remarks
10-29-30	8.51	1.51	Having attacks daily. Very uncomfortable.
11- 7-30	10.9	2.07	November 3, 4 and 5, 15 units parathormone, 90 grains Ca lactate.
11-21-30	9.2	—	Nauseated after last dose. November 11, 13, 10 units. Nauseated.
12- 2-30	11.6	—	Five units November 24 and 28. Much better, eating everything, even eggs. Has gained eight pounds. Viosterol 30 drops twice daily.
2-10-31	15.0	2.3	No parathormone since December 4. Occasional hives, occasional swelling face and hands.
5- 5-31	18.0	—	No hives or angioneurotic edema. Does not eat fish, tea, coffee, nuts, chocolate. Gained two more pounds. Feels quite well. Still taking Viosterol with Ca lactate occasionally.

The parathormone was discontinued and Viosterol and calcium given to her. She herself noticed that all kinds of fish, tea, coffee and nuts caused outbreaks. She also remarked that the blood for the last calcium determination which was 15.0 mgs., was easily obtained, that the veins on the back of her hands were again visible. She had had very little hives and no edema. In April she had a sharp attack of influenza. On May 5th the serum calcium was 18 mgs. She was taking calcium lactate only now and then but had continued Viosterol 30 drops twice daily. She considered herself practically well.

#### COMMENT

There are several interesting features in this case. This woman was born and lived in Nebraska all her life. She had never shown any manifestations of allergy until the sudden onset when she was thirty years old. She reacted to practically all of the food proteins so that she had decreased her diet until she was on starvation rations. Alexander,<sup>10</sup> in a study attempting to evaluate the skin test in allergy, says, "No sufficient data concerning positive reactions in urticaria and angioneurotic edema could be found, but the skin test in these conditions is notoriously unreliable." She was in the hands of expert physicians who had tried all the usual and some unusual therapeutic measures. She chanced to belong to the group of low blood calcium people whose calcium could be raised by the newer method of parathormone plus a calcium salt in large doses.

There is no explanation for her tetany attack when the serum calcium was rising and at a normal figure. When the serum calcium was at its lowest point there was no attack following constriction of the arm. Transported calcium does not necessarily mean available calcium and it may well be that had the diffusible and non-diffusible fractions been calculated some marked abnormal relationship would have been found. It is possible that the parathormone raised the non-diffusible calcium much more than the diffusible, leaving her with some actual calcium deficit. However, this is speculation.

Another interesting feature was the unusual vasoconstriction while the urticaria and edema were appearing daily. Lack of calcium should not cause vasoconstriction. As soon as her symptoms disappeared the vasomotor tone became normal. At the same time, the serum calcium was unusually high. We are still ignorant of many fundamental factors in calcium metabolism.



## SUMMARY

A brief sketch is given of calcium in the body in its relation to allergic disorders particularly to urticaria and angioneurotic edema. A case is described where serum-calcium deficiency was present and the symptoms of the patient were relieved by raising the calcium by means of parathyroid extract (Collip) plus calcium salts.

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# XANTHOMA MULTIPLEX

## With Report of a Case

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THE story of Xanthoma, Xanthomatosis and Xanthelasma has been an interesting one since its first description by Roger in 1836 and the monograph of Addison and Gull in 1851. Many types or manifestations of the condition have been described—thus in an article by Harbitz, he mentions the classification of Aschoff and Kaminer:

A. Genuine Xanthomata.

1. Unmixed xanthoma tumors.

2. Mixed tumors—as fibroma and sarcoma admixed with xanthomatous tissue.

B. Xanthomatous conditions associated with various diseases, diabetes, nephritis, hepatic disease.

C. Pseudo-Xanthomas—*i.e.*, deposits of xanthoma in local inflammatory foci where fat is undergoing absorption.

Siemens, also quoted by Harbitz, makes the following divisions:

1. The development of xanthomatous tissue in the case of metabolic disturbances and often associated with hypercholesterinemia—usually multiple, frequently symmetrical as Diabetes Mellitus, hepatic disease, *etc.*
2. Development of xanthomatous tissue without general disturbances.
  - a. As genuine tumors.
  - b. As pseudo-xanthomatous tumors, *i.e.*, cholesterin deposits in inflammatory infiltration or degenerated tissue.

Harbitz' own conclusions are:

1. Sarcomas of the tendon sheaths (with giant cells and xanthomatous tissue) are true tumors but benign.
2. Circumscribed tumors of the articular capsule or synovial membrane are generally malignant sarcomas.

3. The multiple, often symmetrical pure xanthoma with characteristic localization around the knees and elbows, on the gluteal region, on the hands and feet, along the tendon sheaths and on the eyelids, are not genuine tumors but tumor-like deposits resulting from a constitutional disease and as a rule accompanied by hypercholesterolemia. In such cases sudden death frequently occurs caused perhaps by internal localization, for example, in the heart.

On the other hand, many of the older students in the subject regarded xanthoma purely as a skin disease, others as benign tumors representing fetal rests. Its association with various diseases has been noted and Torok, quoted by Sikemeier reports certain series of cases in families—an extremely interesting observation as regards the later views as to the cause of the disease—an error of metabolism, a predisposition, a diathesis. It has been reported associated with liver and gall-bladder disease (gall-stones, carcinoma, cirrhosis, cysts of the liver), nephritis, diabetes, but in certain of these it is quite possible that the xanthomatosis could have been due to a congenital or acquired error of lipid metabolism—Chauffard speaks of a xanthomatosis diathesis to explain why it is not present in all such cases, and Gilbert accents its hereditary tendency.

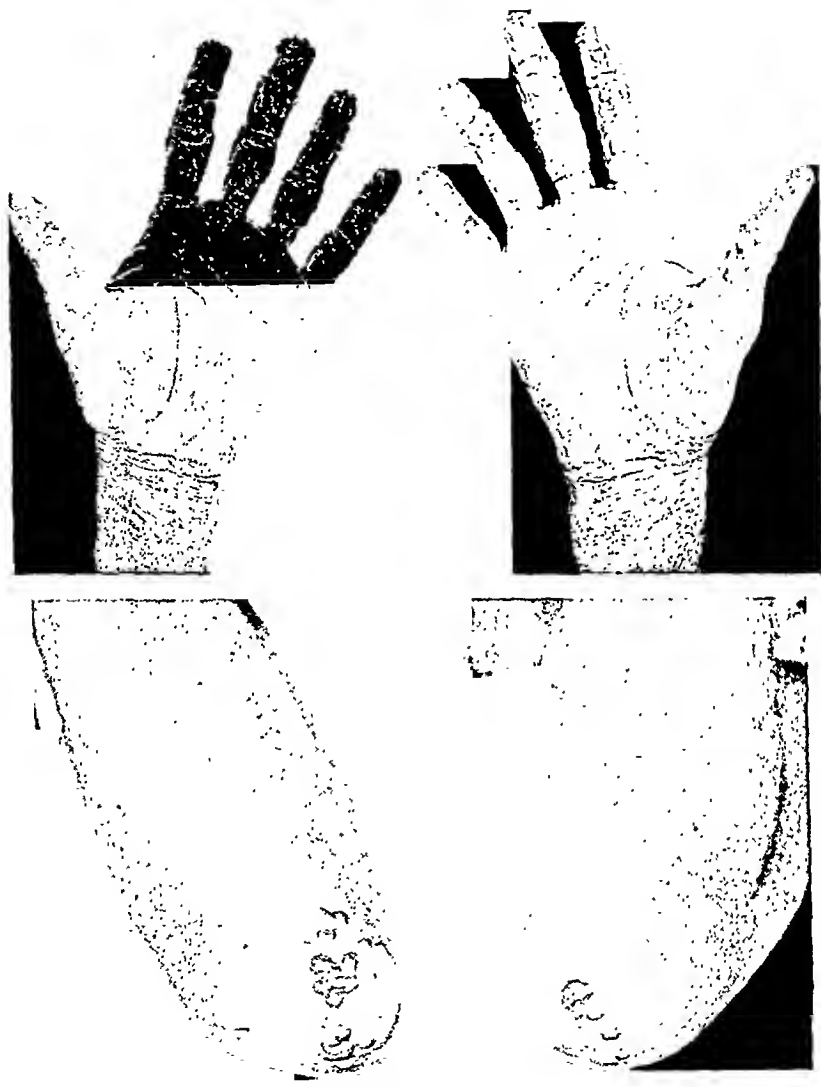
Sikemeier in his paper on the chemical studies has drawn attention to the relation of the disease to fatty metabolism and the close relationship or identity of the xanthomatous tissue to a bipolarizing cholesterol ester, to the observations by many of hypercholesterolemia in true cases of the disease and to Chauffard's conclusion that xanthomatous masses are cholesterol infiltrations of the skin analogous to tophi in gout and probably due to lipolytic insufficiency of the pancreas, while Hutchinson and others explain its presence in pelvic disorders and pregnancy by the hypercholesterolemia met with in these conditions; Chvostek, on the other hand, believes that certain of its manifestations can only be explained by a disturbance of the sympathetic nervous system. Sikemeier himself reports a case associated with what he regarded as tuberculosis of the liver and suggests that this may be a frequent cause—highly improbable from a study of the literature. Is it not more likely that the liver nodules might not be tuberculous but xanthomatous deposits and that, in certain cases in which liver and gall-bladder disease are regarded as primary, in reality the xanthomatous deposits are primary—the hepato-biliary pathology secondary?

Futcher in reporting three cases of xanthoma multiplex asso-

had no menstrual flow for six months. There had been no prolonged bleeding, metrorrhagia or flushing prior to the major trouble of which she complained. The patient had had no operations.

In the spring and summer of 1929, following a period of unusually hard work and concomitant nervous strain, the patient first noted increasing weakness; during the fall of that same year she began to lose weight. In the winter and spring of 1929-30 her friends remarked that her color was "bad" and in March, 1930, she became distinctly jaundiced without having had real pain. A number of medical biliary-drainages were without striking result and on April 19, 1930, she submitted to an exploratory laparotomy at the advice of her local surgeon. He reported that he had found a catarrhal inflammation of the appendix and gall-bladder and that he had done an appendectomy and cholecystectomy. He had noted no gall-stones in the gall-bladder, or in the common and hepatic ducts. The liver was markedly enlarged and "nodular," i.e., "nodules" were scattered throughout its substance. None of these were removed. The pancreas he found to be normal; no primary carcinoma was discovered. Directly following this operation the patient developed cream-colored thickenings of the skin about the knuckles, the palms, the elbows, the heels, the bridge of the nose and the neck and back. Later this same process involved the vulva. There were never signs of inflammation about these lesions. Often the patient pierced them with a needle thinking that they contained pus or sebum but blood only had been obtained. The lesions were tender to pressure and her only discomfort from them was caused by trauma. After the operation the jaundice became deeper for a time; then it cleared slightly and for a year it had seemed to vary from time to time, appearing to be deeper when she was fatigued. At no time did she have chills or fever. In June, 1930, the patient began to have eight to ten clay-colored foamy stools a day. This lasted for about two months and it had recurred off and on but it had never been severe or prolonged after the initial attack. Since the appearance of jaundice the patient had been annoyed by flatulence and flatus and occasionally there was some slight abdominal discomfort from gas. There was no pain, nausea or vomiting at any time. After her operation she continued to lose weight and because her jaundice persisted the patient consulted Dr. E. D. Shanks of Atlanta in August of 1930. He has kindly sent us reports of his examinations at that time. He found the patient to be distinctly jaundiced and he noted extensive xanthomata over the palms and knuckles and back. The teeth were decayed and loose and there was definite pyorrhea. The liver edge could be felt two fingers' breadths below the costal margin, its upper border was percussed at the fourth rib. The spleen was not palpable. On pelvic examination an atrophied uterus was found and there was tenderness in the right side of the pelvis. The blood count made in August, 1930, showed a hemoglobin content of 70 per cent., the red cells were 3,110,000 and the leukocytes 7,950, with a normal differential count. A fragility test done by Doctor Shanks was normal; the Wassermann test was negative. The blood non-protein nitrogen was 35 mgs. per cent., the blood sugar 108 mgs. per cent. and the van den Bergh test showed an immediate direct reaction. Complete X-ray examinations of the stomach at that time revealed an atonic stomach and duodenal cap, both of which emptied in five hours. The colon was spastic and films showed no filling defect. A chest plate failed to show evidences of pulmonary tuberculosis.

FIGS. 1 and 2.



Hands and elbows of patient afflicted with xanthoma multiplex.



During the winter of 1930-31 (synchronous with a period of six months of amenorrhoea) the patient improved slightly. On forced feeding she gained from 103 to 109 pounds and her appetite, which had been rather poor, improved. In March of 1931 the patient had a painful, rather prolonged menstrual period. With this she lost weight and her appetite again became poor. Since March she had menstruated irregularly and had held her weight at 105 pounds by forced feeding.

June 22, 1931, at our physical examination, one saw a thin woman with a moderate degree of jaundice and anemia. On both lids were definite xanthomata. Larger xanthomata were noted on the knuckles, the palms, the elbows, the back, the heels and the vulva. There was no inflammation about any of them. The skin over the fingers was dry and tended to crack. The xanthomata on the palms seemed to follow the course of the vessels and lymphatics. The eye reactions were all normal. Many teeth were missing and those that remained were in poor condition. There was definite pyorrhea and the gums bled easily. The tonsils were small and were not inflamed. There was no enlargement of the lymphatic glands or of the thyroid. The pulse was slow and regular; the vessel was not palpably sclerosed; the blood-pressure was 103/66. On physical examination the lungs were normal. There was no enlargement of the heart and the cardiac sounds were normal except for a faint systolic blow at all the valve areas. The costal angle was narrow and the abdominal wall was atonic. The liver edge could be palpated four fingers' breadth below the costal margin in the right mid-clavicular line. It was sensitive and seemed finely nodular. To percussion hepatic dullness began at the fifth rib. The spleen on deep inspiration reached two fingers' breadth below the rib margin; it was not tender. Both kidneys were a little ptosed. A spastic descending and sigmoid colon was palpable. There were no abdominal masses. The ankles showed no edema; the knee jerks were normal. Pelvic and rectal examinations revealed nothing of note. (Figs. 1 and 2.)

Voided urine contained a trace of bile, a very slight trace of albumin and a very few pus cells; there was no sugar. The hemoglobin was read at 56 per cent., the red blood-cells were 3,040,000 and the leukocytes 7,400. The differential count was normal. The platelets were 370,000 per cu. mm. The Wassermann was again negative. The van den Bergh reaction was positive in both direct and indirect reactions. The red cells were distinctly resistant to hypotonic salt solution and hemolysis was not complete in 0.28 per cent. sodium chloride solution. The coagulation time by the method of Lee and White was first fifteen minutes and later was checked at twenty-two minutes (normal five to ten minutes); the bleeding time was four minutes. The blood non-protein nitrogen, uric acid and sugar were normal. The serum cholesterol was 1000 mgs. per cent., about five times the normal. Forty-five minutes after ingestion of an Ewald meal no free hydrochloric acid was found in the stomach content and the total acid was six. Diagnostic biliary drainage yielded no "B" bile. The light-colored bile obtained showed a very few pus cells, no crystals and no calcium-bilirubin pigment. On this duodenal fluid the diastatic activity was measured by Martin's method. It contained 67.2 units (normal is 40-70). It was not tested for tryptic or lipolytic activity. Stool examinations revealed no parasites and a stain with Sudan III was negative for neutral fat. The

benzidine test for occult blood was positive but was made on a specimen obtained the day following gastric gavage and duodenal drainage. An intra-dermal tuberculin test (0.1 cc. of a 1:2000 dilution) was negative.

Fluoroscopic examination of the patient's chest was normal. The stomach was atonic and ptosed and the colon seemed atonic at the time of examination.

From the elbow, skin was excised for chemical and histologic examination of the xanthomata. Dr. E. M. K. Geiling reported large amounts of cholesterol in the nodules. He found no bile-salts or reducing substances. Sections for histologic study were reviewed by Dr. W. G. MacCallum, who confirmed the diagnosis of xanthomata.

#### SUMMARY

In the case of xanthoma multiplex reported by us there are certain factors of peculiar interest:

1. The fact that the general symptoms preceded by one year the onset of jaundice makes it appear probable that in this case at least the biliary tract disease was *secondary* to the xanthomatosis, especially as at the operation performed one year before the patient was seen by us no gall-stones or gross pathology of the gall-bladder was found, while the diffuse nodules found at that time in the liver were probably multiple xanthomata as the subsequent history of the case make it highly improbable that they were carcinoma or tuberculoma.

2. As to the cause of the hypercholesterolemia in this case we have no exact or satisfactory explanation; we could get no family history of similar conditions, but the age of the patient and the very definite menopausal symptoms suggest that the latent tendency might have been brought to the surface by this means.

3. The figures for blood cholesterol, 1000 mgs. per 100 cms. are, as far as we know, the highest yet recorded in this condition; the highest figures mentioned in Rowland's very complete study of the literature were about 600 mgs. The blood cholesterol estimations in our case were made in the Chemical Laboratory of the Medical Department of the Johns Hopkins Hospital and as they were so high were repeated and the same figures obtained.

4. The gastric achlorhydria (test meal showed free Hcl 0, total acid 6) probably is toxic in origin due to the hypercholesterolemia, and thus is probably very similar in nature to the gastric achlorhydria so common in chronic gout.

5. The rarity of the condition, the interesting clinical and lab-



oratory findings, certain rather unusual features of the case and the ever-increasing interest in the problems concerned with the inborn or acquired errors of metabolism are the reasons for this paper.

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# THE PROBLEM OF PRECORDIAL PAIN

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THIS subject was chosen for discussion not because there seemed anything very new to say upon it and not because what was said could be said with much assurance, but it was chosen because the subject has always been one of unusual difficulty and some of the problems presented by it seem almost insoluble; for though from the days of Heberden until now a well-defined sector of knowledge, gradually increasing in breadth, has been cut out of a large circle of ignorance, yet after much labor by many writers upon the subject one might say, in the words of Omar Khayyám:

"Myself when young did eagerly frequent  
Doctor and saint and heard great argument  
About it and about, but evermore  
Came out by the same door that in I went."

Diseases which give visible, tangible and palpable physical signs, or which either the X-ray or chemical evidence will reveal, have much of their mystery uncovered, but those which depend for their identity on what the patient feels or says he feels can masquerade under any name and almost defy detection, and herein lies the essential problem of precordial pain.

Experience has taught us that a certain kind of precordial pain coming on in a certain way in certain kinds of people may mean a grave, even fatal disorder, but experience has also taught us that a very similar kind of pain in other kinds of people may mean little or nothing. Thus it may happen that the person whom we have assured that his pain means nothing, may die on our doorstep, and the one we wrongly guessed had a fatal malady may relate to a fellow mourner at our funeral how he outguessed us years ago.

Of all the causes which have beclouded the issue none is more potent for evil than the names which have been put upon precordial pain.

The name "angina" means a clutching at the throat; thus we have scarlatinal angina or Ludwig's angina, and all the other sore throats. On account of the clutching quality of chest pain this was called angina pectoris, or clutching at the breast. Then there followed true and false clutchings at the breast—in other words, clutchings which clutched and those which didn't clutch—then angina sine dolore or painful clutching without pain, and again angina vasomotoria, or vasomotor clutching of the chest, all of which stir up a feeling of great confusion.

Again, through all the confusion of tongues, the word angina appears, fraught for generations to the patient with the same meaning as the skull and cross bones. Whether we told a person he was to be victim of true murder or false murder or painless murder or vasomotor murder, it would be *murder* and not any of its assuaging phrases that would stick in his mind, and so with the word "angina"—meant first to carry the concept of a type of cardiac pain, it means now to the patient sudden, painful and early death.

With that vagueness of its clinical meaning and the terror which it carries its use in this age of the world seems as cruel as it is unscientific. But since the term angina pectoris has for generations been synonymous with a type of precordial pain, it may be well at this time to summarize the views of the late Sir James MacKenzie upon the significance and content of its symptom complex, and I ask your forbearance while I do this at some length.

Angina pectoris, in the view of MacKenzie, was a condition in which certain symptoms are produced by the heart, of which pain is the most prominent. The pain appears in attacks lasting for seconds or minutes, but sometimes for hours, and gradually passing off. Other symptoms accompany the pain, such as a severe constriction of the chest, a feeling of great depression, pallor or flushing and a flow of saliva.

The pain is limited to the front of the chest and arms, most frequently the left, and may appear in the jaws and neck and behind the ears. It has been shown that pain as such is felt only in areas supplied by the cerebrospinal system of nerves, and when it arises in a viscus, it is perceived as pain only by means of the connection of that viscus with the cerebrospinal fibers distributed to the body wall, corresponding in segmental area to the organ involved. Again,

pinching or pressing a viscus does not give rise to pain, but pain is produced by contraction of the muscle of the viscus, and it comes about when the contractions are unduly strong or when the organ is poorly supplied with blood, or when a third factor makes the central nervous system unduly sensitive.

This, then, in MacKenzie's opinion allows one to divide angina into primary—where the stimulus arises from damage in the heart muscle—and secondary, where a normal stimulus from the heart is exaggerated by a hyperactive receiving depot in the central nervous system.

MacKenzie would regard heart failure as the condition in which the heart is no longer able to meet the demand for efforts necessary to the daily life of the individual, and the symptoms of heart failure are found to arise on the one hand from the respiratory system which feels the failure of the heart's output and responds by breathlessness, and on the other hand from the nervous system in the form of pain following effort.

Even a healthy heart will eventually fail and show symptoms if effort is severe enough; a healthy heart muscle embarrassed by damaged valves or by an abnormal rhythm will fail sooner, and a muscle damaged by age or by poisons or by a poor vascular supply will fail still sooner, and each when it fails will give rise to the symptoms of failure usually by shortness of breath or by pain.

Pain is of value to the clinician in helping him to localize the site of disease, for certain general symptoms as fatigue, fever, loss of appetite, malaise and rapid pulse are common to many diseases, but *pain* offers a clue to the organ involved. This is particularly true of the types of colic—biliary, renal, uterine, appendicular and cardiac, each of which may give rise to vomiting, sweating, collapse, *etc.*, but the *pain* in each has a distinctive quality and often points to the organ involved, and what is true of pain is even more true of hyperalgesia of the body wall.

It would be unreasonable to suppose that the ureter or the cystic duct or the bowel or the heart had each a special central mechanism for the registering of pain sensations, which mechanism might or might not ever be used.

It would, however, be quite reasonable to presume that an exaggeration or an aberration of normal contraction might, through the

ordinary nervous connections, register itself as *pain* referred to the body surface appropriate to the organ concerned.

Abnormality of contraction in a visceral musculature may give rise not only to pain but to skin hyperalgesia and also to muscular contraction in the same area of cerebrospinal distribution, as well as to such autonomic reflexes as vomiting and sweating, and to vasomotor reactions as pallor or flushing or collapse or to such movements as the swallowing of air.

The contraction of heart muscle in the presence of a diminished blood supply is an efficient cause for cardiac pain.

The commonest cause for diminished blood supply to the heart muscle is damage to the coronary arteries.

The significance of hyperalgesia, which is fairly common after attacks of cardiac pain, as also after biliary and renal colic, is that the central nervous system after the barrage of painful sensations has remained irritable and reacts with pain after a relatively slight tactile stimulus in the cutaneous area concerned, and at times pressure upon this area may cause a repetition of the cardiac pain.

For the heart this area is the one supplied by the cerebrospinal nerves from the eighth cervical to the fifth thoracic segment.

These spinal nerves are distributed to the external body wall of the chest down to the level of the fifth interspace in front, and into the axilla and down the inner side of the upper arm and the ulnar side of the forearm to the little and ring fingers and also over a corresponding portion of the back of the chest.

The chief signs of gravity in cardiac pain are the readiness with which the attack is provoked and the extent of the patient's limitation of response to effort.

In 284 cases of angina recorded by MacKenzie he found that 120 had died suddenly, nine died of apoplexy, two of gangrene of the feet, two from aneurysm and one from uremia.

The greatest number died between sixty and sixty-five, and two-thirds of all the deaths occurred within three years from the first attack of pain. In forty postmortem examinations most of them showed marked changes in the coronary arteries.

From the point of view of diagnosis a few points clearly emerge:

(1) The symptom group of substernal pain brought on by exer-

tion or by excitement in a man above middle life, and radiating down the arms or to the neck, accompanied by anxiety and respiratory oppression, and subsiding with cessation of effort or under the administration of nitrites, usually indicates coronary disease.

(2) The same picture may result from aortic syphilis.

(3) It may occur when no coronary disease nor aortic syphilis exists.

(4) Our attention should then not be focused exclusively upon the *type of pain* in an effort to distinguish between a so-called true angina and a false angina but rather upon those signs which identify coronary sclerosis or obstruction or actual aortic disease.

It is unusual for coronary sclerosis to exist without one or more of the following signs: (a) The evidence of arterial disease elsewhere, as noted in the radial, temporal or retinal arteries. (b) Some elevation of the blood-pressure. (c) Hypertrophy of the heart or accentuation of the second aortic sound. (d) X-ray evidence of cardiac or aortic widening. (e) Electrocardiographic evidence of myocardial damage. (f) Clinical or serologic evidences of syphilis.

If one or more of these are present in a case presenting the history of cardiac pain, wisdom will dictate a diagnosis of coronary disease.

If they are all absent, we are unable to make a diagnosis of coronary disease and must either take the bull by the horns and make a diagnosis of a healthy heart or continue our observations until more evidence appears.

Another type of precordial pain has been noted by Barnes and Willius, who report seven cases of paroxysmal tachycardia in which pain of so-called anginal character appeared during the paroxysm.

It was not relieved by nitrites but was relieved by morphia and it disappeared with vomiting and did not return during the interval between attacks. Most of these patients were subjects of hypertension.

The prognosis was no worse than in uncomplicated tachycardia.

Of analogous character are the cases in a group of five reported by Schwartz in which paroxysmal cardiac pain occurred in patients of from fifteen to twenty years of age, the subjects of chronic rheumatic heart disease. There were violent seizures of precordial pain with violent palpitation, severe headache and various vasomotor phenomena, marked pulsation of the peripheral vessels, paroxysmal

rise in blood-pressure and increased pulse and respiratory rate and no rise in temperature, but signs of decompensation were usually absent. The seizures varied from six to sixty a year and lasted for from half an hour to an hour and a half and were rather improved by effort. The blood-pressure readings were strikingly high, often reaching 275 millimeters systolic. The rise was sudden and the fall slow. The liver did not enlarge nor the lungs fill up.

I recall such a case as this in a young French-Canadian boy with mitral stenosis occurring in the service of the late Doctor Molson.

Schwartz reports four of his cases alive, at one, five, six and eight years after the onset of attacks.

*Coronary thrombosis* with cardiac infarction has been recognized by the pathologists for a long time, but Herrick's paper in 1912 made it known as a clinical concept in this country and showed that it was not always immediately fatal and not always even fatal.

As showing its relation to the type of precordial pain already discussed I think of the case of a clergyman of fifty-four years who for three years had had pain in the left arm and left pectoral region coming on after exertion but relieved by a few moments' rest. His only physical signs were a slight muffling of the cardiac first sound and accentuation of the aortic second sound and a blood-pressure of 140/85, but his electrocardiogram showed some inversion of the "T" wave in the second lead.

A diagnosis of coronary sclerosis was made and gradually his field of response became limited so that after walking three hundred yards his pain appeared.

One Sunday night he preached from the text "I have fought a good fight. I have finished my course. I have kept the faith" and went to bed at 11 P.M. At 1 A.M. he was wakened with an excruciating pain in his left arm. I saw him shortly afterward in a state of collapse, ashen gray in color, cold and sweating and nauseated, with an unbearable pain in the left arm but with no dyspnea. The heart sounds were inaudible and the blood-pressure would not register. He was perfectly conscious up to the time of his death sixteen hours later. Amyl nitrite had no effect on the pain and morphia even in large doses did not completely relieve it.

His would appear to have been a case of coronary sclerosis with ultimate thrombosis and occlusion.

Another instance concerned a man also of fifty-four who for ten years had been developing an increasing hypertension with evident arterial sclerosis.

For over a year before his fatal illness he had suffered from occasional attacks of pain in the precordium and left arm, brought on by exertion and relieved immediately by trinitrin.

One night he developed while in bed an attack similar in location but of much greater severity and associated with faintness, pallor and nausea. Three hypodermics of one-quarter grain morphia each did not completely relieve the pain. The pulse became rapid and intermittent, the heart sounds very feeble and the blood-pressure which before had averaged 180/110 dropped to 130/80 and never rose above this for the balance of the year and a half which he lived. The day following his attack he developed a pericardial friction and a temperature of 100.4° which remained up for several days. Some time later another attack of similar nature developed and following this an embolism of the posterior tibial artery, but the leg gradually regained its circulation.

Still later he suddenly developed a right-sided hemiplegia with aphasia without loss of consciousness and was confined to bed and chair until his death, but never had any further precordial pain.

The course of events here was apparently a general arterial sclerosis with coronary sclerosis, coronary thrombosis with cardiac infarction involving the thickness of the ventricular wall and formation of a mural thrombus on the inner surface of the ventricle; femoral, and later cerebral embolism, and finally such a degree of physical disability that even the greatly damaged heart was not taxed beyond its power.

The pain of coronary thrombosis is not always praecordial nor precordial only.

Some years ago a man of fifty-eight who had had many attacks of cardiac pain, and had also suffered much from indigestion, had a particularly severe attack of acute pain and tenderness and muscular spasm over the gall-bladder area with no substernal pain but with vomiting and fever and leucocytosis and profound collapse. The blood-pressure was 165/130. The heart sounds were clear but distant and the pulse was 20, and we attended ourselves to a diagnosis of coronary thrombosis. I saw, Doc and I felt certain that



in addition he had an acutely inflamed, probably gangrenous gall-bladder, and his abdomen was opened and the gall-bladder found full but with no acute cholecystitis. He next morning developed a pericardial friction and died about twenty-four hours later with a most extensive cardiac infarction from coronary thrombosis.

Faulkner, Marble and White, of the Massachusetts General Hospital, investigated the clinical resemblances between coronary thrombosis and gall-bladder disease by means of the comparison of the histories of thirty cases showing postmortem evidence of practically complete coronary occlusion, with thirty cases of gall-bladder disease confirmed by operation.

They found that none of the cases of coronary occlusion were diagnosed before admission to hospital and only three after admission, while twenty-six of the gall-bladder cases were diagnosed on admission. (Several years ago.)

The youngest case of coronary occlusion was forty-two and the average age was fifty-eight years. The gall-bladder cases averaged forty-seven years. The duration of symptoms in the coronary cases was six months, in the gall-stone cases twenty-eight months.

Coronary occlusion occurred four times as commonly in males as in females, while cholelithiasis occurred four times as often in females as in males.

To sum up the clinical features, one may say that in a man of fifty or over who may have had substernal or precordial pain which he has perhaps attributed to gas on the stomach, who develops an acute pain in the chest, perhaps spreading to one or both shoulders or arms or neck or jaws or to the upper abdomen, with signs of collapse and nausea, with feeble pulse and feeble heart sounds, and a lowered blood-pressure, and in whom the pain lasts a half an hour or more and is not relieved by nitrites and only relieved by large doses of morphia, and in whom after a few hours' rise of temperature, leukocytosis and a pericardial friction develop, has in all probability an occlusion of the coronary artery; but the essential element in diagnosis is the recollection of the fact that *such a disease exists*.

It is much commoner than has been supposed, and R. L. Benson, of Portland, Oregon, in 1,750 autopsies on coroner's cases, found fourteen cases of rupture of the heart, as well as forty-six recent infarcts and eleven healed infarcts and nineteen cases of cardiac

aneurysm, making seventy-two cases in all due to coronary occlusion, or 4 per cent. of all cases of sudden death among the civil population.

The coronaries are only partially end arteries, anastomosis being common when partial blocking from sclerosis has taken place so that sudden blocking of a healthy vessel is a graver event than blocking of a sclerotic one and is more commonly a cause of sudden death.

In earlier days, the dramatic onset and frequently fatal ending of cases of coronary occlusion caused them to be mistaken for cases of poisoning, and there is little doubt that some exalted personages in history whose high living and plain thinking might have earned for them a degenerative arterial disease actually did die from this disease and not from a secret potion administered by some fine Italian hand.

As late as our own time the acute indigestion which carries off elderly people with great suddenness is also coronary thrombosis, and thus "acute indigestion" might be well described as the disease which never happens but often kills.

In passing, one may comment upon the impression that is so common that pain in the chest is caused by indigestion because it is relieved by the belching of gas.

The boot is on the other foot. People who suffer from cardiac pain may also have, as a reflex result, swallowing movements, which fill the stomach with air, and the expulsion of this air gives a natural feeling of relief, and what is actually an effect comes to be regarded as a cause.

In connection with the coronary artery distribution, Wearn demonstrated that the Thebesian veins were a source of collateral circulation. He perfused hearts recently removed and found that dye injected into the coronaries ran into the chambers of the heart. He also reports two cases which at autopsy showed occlusion of both coronary arteries of long standing and these hearts must have received nutrition from the chambers of the heart through the Thebesian veins.

These facts emphasize the necessity for long periods of bed rest in cases of coronary obstruction in order to allow compensatory circulation to develop.

We may pass quickly over aortic syphilis as a cause of precordial pain, for here he who runs may read. Physical signs, the X-ray and serology all unite upon the diagnosis. The same may be said

of the various forms of pericarditis, though one must admit that the signs of its presence are not always appreciated, though they are there for those who seek.

The most difficult group of all is the one in which a good and sometimes perfect picture of coronary disease is given by those people in whom no evidence of heart disease can be found.

I will briefly cite three cases.

A man of fifty-eight with considerable business responsibility complained that for four weeks he had noticed some numbness down the left arm after walking for some distance. On sitting or standing this discomfort would pass away. He also noticed that he became short of breath on slight exertion, at which time, also, a pain in the chest would come on.

The pain he described as a dull ache with a sense of tightness or compression around the chest.

Another pain under the sternum he described as a sense of fullness in the stomach.

He found that it required much less exertion then to bring on the pain than it did at first.

On examination all of his systems were found to be normal. The blood Wassermann was negative. The X-ray examinations of the heart and of the gastro-intestinal tract after a barium meal and of the gall-bladder after intravenous Iodeikon were normal.

The blood chemistry was normal and the electrocardiogram showed a normal tracing with a rate of 84 and the blood-pressure was 120/82.

This patient was laboring under a considerable strain and some apprehension, and, in spite of his typical history, the diagnosis was made of a healthy heart and the subsequent course has justified the diagnosis.

One other type of precordial pain occurred in a graduate nurse of twenty-nine years, who, two years ago, after a fatiguing case, while getting a drink for a patient, was seized by a sudden pain over the area of the heart lasting a few seconds.

She called for help and kept her hand pressed over her heart. She was told that she turned an ashy pallor and that her lips were blue and her pulse 160.

She had fairly frequent attacks of this sort which came on while

she was in bed and the pain radiated into the axilla and down her left arm. All of the attacks appeared during the menstrual period and were associated with great weakness and palpitation and frequently numbness in both hands and both sides of the face. In one attack she lost her speech for five minutes and vision became dim and she vomited.

On examination she had a persistently rapid pulse—about 100—a blood-pressure of 115/80 and a soft apical systolic murmur. Examined during an attack of pain an observer would not realize that she was suffering.

The electrocardiogram was essentially negative, the basal metabolic rate normal and the X-ray showed no increase in the size of the heart and the blood Wassermann was negative. There was a practically complete left-sided hemianesthesia and the pharyngeal reflex was absent. It was felt she had no organic disease of the heart as a cause for pain and that the condition was of the nature of a neurocirculatory asthenia.

With the assurance that she did not have angina pectoris she steadily improved and went to work.

Another case which gave rise to much difficulty in diagnosis was that of a man of fifty who had been a hard-working outside man, a moderate user of tobacco and alcohol but otherwise with a negative history.

He was perfectly well until September, 1925, when he found that on exertion he got a tight feeling in his throat which disappeared on rest. Two months later this feeling spread until, on walking half a block, he had a feeling as if the chest were gripped in a vise.

This feeling was most marked under the sternum and radiated to both shoulders and down to the epigastrium. The pain passed off in two minutes after ceasing exertion. There was no vomiting nor sweating. Physical examination was negative. The blood chemistry and serology were normal. The cardiogram showed a normal tracing but in the gall-bladder on X-ray examination was a large solitary stone.

In view of the negative cardiovascular findings, he was advised to have the gall-bladder removed, and following this procedure there was gradual improvement, and after one and one-half years he became quite free from symptoms and now, five years later, can walk any

distance and indulge in any activity without discomfort, and his pain has become a memory only.

Aside from gross damage to the coronary arteries, which renders them incapable of furnishing the heart with sufficient blood for its normal metabolism and thus gives rise to cardiac pain, we have to recognize a relative insufficiency of coronary outflow, of which the following examples may serve. Carey Coombs and others have noted the prevalence of anginoid pain in pernicious anemia. Here the coronary outflow may be sufficient in quantity but low in quality and in such cases the raising of the blood value through liver therapy may cause cessation of cardiac pain.

Thyrotoxic patients with cardiac pain have obtained relief from their pain by removal of the toxic goiter, by which means the actual metabolism of the heart muscle was abruptly lessened and the coronary supply became adequate for the new condition.

Conversely, in myxedema, in which disease vascular sclerosis is common, typical cardiac pain may develop under thyroid therapy; here the damaged coronary circulation was competent for the limited demand upon it but is now unable to meet the call of the increased metabolism in the myocardium, brought about by thyroid administration.

Again, hearts which are free from pain under ordinary circumstances may respond with pain to the injection of epinephrin.

Though the question of diagnosis has been touched upon in what has been already said we may now return to it again.

Enough has been said to indicate that precordial pain may result from many different causes and this statement is true also of the symptom complex commonly called angina. Here may I digress for illustration to a case described by Dr. Philip King Brown in which a physician of seventy-one had his first major attack (angina) of cardiac pain at fifty-eight. He had eight others as well as almost daily attacks of minor character and six years ago had a well-defined attack of coronary thrombosis. He said that all of the attacks differed only in their severity and duration.

In the two fatal cases which I have cited above, the same could be said.

Let us digress again, this time in search of analogies. The symptom complex described by Moynihan of hunger pain, food ease

and nocturnal pain, which he regarded as pathognomonic of duodenal ulcer, may be simulated and even duplicated in gall-bladder disease and appendicitis, and fairly closely imitated, in some purely psychic disturbances.

One does not, however, found a diagnosis and a prognosis and a therapy upon this pain alone but seeks by all means available for a definite anatomic diagnosis.

Similarly, in precordial pain, while a large proportion of the pains coming on with exertion, radiating to the arm, *etc.*, and relieved by nitrites, are due to coronary disease, some are not, and before we attempt to name the disease we should try by every method known to medicine to make an anatomic diagnosis, and it will be rarely that either physical examination, X-ray, serology or the cardiogram, the blood-pressure instrument or the ophthalmoscope will not set us on the right road.

In the absence of evidence implicating the heart or its vessels anatomically, we are not justified in giving a grave prognosis any more than we would be justified in calling a case duodenal ulcer which had a suggestive history of pain, but no proof in physical, chemical or radiologic examination.

The name angina should take its place with indigestion, biliousness, hyperacidity and neurasthenia among symptoms and not among diagnoses.

*Treatment.*—This implies diagnosis. In the case of coronary sclerosis the treatment is almost stereotyped but a few things may be said.

Pain like dyspnea is a sign of cardiac deterioration and what the heart could do once, it can't do now.

Safeguarding by means of diminished output of energy is the keynote and in this instance the treatment is automatically applied.

In some instances a long period of bed rest has been tried but the results have not been dramatic.

Relative rest by means of a later hour of starting work, an earlier hour of quitting, with a longer break at noon and rests after meals and by a long night's rest is of great use.

The avoidance of mental worry—easy for those who have none—is a *sine qua non*. Remember John Hunter.

Residence in an equable climate prolongs life.

A moderate protein intake with small meals and the tabu upon exertion shortly after food are necessary restrictions.

A brightened mental outlook. Hamman tells of a man who lived for two years in great comfort after adopting Christian Science, and we are all reminded of Dr. James Stewart who in speaking of cardiac drugs said "But the greatest of these is H-O-P-E."

If one can lift from a patient the curse which some one has pronounced upon him by calling his disease "angina," he has done one good turn that day.

For medication, the theobromine derivative metaphyllin or euphyllin 0.1 Gm., three times a day, has been useful and no one could get along without trinitrin or sodium nitrite or amyl nitrite for the attacks of pain.

If the diagnosis of aortic syphilis has been made, cautious anti-luetic treatment is obviously indicated.

Coronary thrombosis demands morphia in large doses. The nitrites are useless and may be harmful in the acute attack. Rest should be absolute and after the first crisis is over a period of weeks should ensue before the patient is allowed up, in order to encourage the maximum collateral circulation.

A patient may live for months or years but always with the sword of Damocles suspended above him.

The prognosis of coronary sclerosis simply cannot be made.

Some clue may be obtained from the degree of exertion required to bring on the pain.

In some the symptom of pain may completely disappear. I know one lady now of seventy-eight whom I saw ten years ago with general arteriosclerosis and typical coronary pain who for eight years has had no attacks of pain.

In some selected cases in which medical measures have failed and where there is great and frequent pain, surgical treatment may be resorted to.

Operative treatment of severe precordial pain was first proposed by Francois Franck in 1899 and first practiced by Jonnesco in 1916 with the idea of abolishing the nervous arc between the heart and the sensorium, thus abolishing pain as a symptom. It is a symptomatic method analogous to the division of the sensory root of the fifth nerve in Tic douloureux.

Jonnesco first removed the upper three cervical and the first thoracic ganglia on both sides.

In 1923, Coffey and Brown, of San Francisco, in five cases claimed that removal of the superior cervical ganglion or division of the main branch going to the heart was sufficient.

The whole innervation of the heart comes from paired vagus and sympathetic nerves. In regard to the vagus there are certain afferent fibers in it spoken of as the depressor nerve. These for many reasons are not likely to carry painful sensations from the heart.

In the sympathetic there are sensory fibres which run from the heart as high as the middle cervical ganglion, no sensory fibers are found above this level, and the superior cervical ganglion and its branches have for the heart only a motor function.

The sensory fibers, whether reaching primarily the middle or inferior cervical or the stellate ganglion, eventually end in the stellate ganglion from which emanate direct sensory fibers leading to the spinal cord. There is no such spinal connection above this level.

Coming away from each ganglion toward the heart we have in sequence the superior, middle and inferior cardiac nerves.

To arrest, therefore, the passage of stimuli from the heart to the central nervous system, one must consider the destruction of the nerves from the heart which reach to the lower and middle cervical ganglion as well as to the stellate ganglion.

The views of Head and Sherrington being that non-specific impulses enter the spinal cord and because of their intensity overflow and stimulate the sensory nerves of that region, the impulses which set up precordial pain must reach the cord in either the lower cervical or the upper dorsal segments.

In 120 collected cases of attempts at relief of anginal pain by surgical means Cutler gives the following summary:

In nine cases of the complete Jonnesco procedure—ablation of sympathetic ganglia and cords on both sides—there was complete relief in all cases and no mortality.

In eighteen cases of left-sided ablation of the sympathetic cord in cervical and upper dorsal region, complete relief in eight cases, improvement in five, no result in two and three deaths.

(It will be apparent, of course, that deaths would likely occur in



the group of unilateral cases as those surviving for a second operation would be better surgical risks.)

Various partial operations on various ganglia and nerves fifty-three cases, with good result in 41 per cent., improvement in 35 per cent., no result in 11 per cent. and deaths in 7.5 per cent.

Posterior nerve root procedures twenty-six cases, with twenty-six doubtful improvements.

In operations involving the superior cardiac nerve 35 per cent. gave good results and 37 per cent. more were improved; in the Jannesco procedure 62 per cent. gave good results and 19 per cent. more were improved.

Thus, interfering with motor pathways to the heart is not so successful as interfering with sensory pathways.

The fact that relief is not uniform suggests there is still some unknown factor.

Richardson and White compared sympathectomy with paravertebral injection on the basis of eighteen cases in which sympathectomy was done, and eight cases in which by puncture in the paravertebral region the upper four dorsal and lower cervical nerve roots were injected with alcohol after they emerged from the cord.

Among the sympathectomies two died, four were definitely relieved and four were failures. In only one case out of the five did a satisfactory result follow a left superior cervical ganglion operation.

In the eight paravertebral alcohol injections there was substantial relief in all cases and complete relief in three cases, with no fatalities and no evidence of further damage to the heart was noted as a result of the removal of the warning pain sensation so that on the whole, injection appears safer than open operation.

Other writers have called attention to the distressing hyperesthesia over the chest lasting two to six weeks after anesthesia has worn off.

Improvement of the cardiac pain has continued for six or seven months after injection and a number of patients have returned to work.

In closing one might make the following summary:

There is a very definite symptom complex including precordial pain which in the majority of cases is due to coronary artery disease.

This symptom group may be produced by other organic vascular diseases, notably aortic syphilis.

It may also be found in people in whom no coronary disease exists, occasionally in gall-bladder disease and in some cases with no demonstrable disease. Every effort, therefore, should be made to arrive at an anatomic diagnosis rather than a diagnosis from symptoms.

Coronary occlusion has a well-defined clinical picture distinct from coronary sclerosis and is not always a fatal disease.

Precordial pain may occur in rheumatic cardiac disease and in paroxysmal tachycardia.

The treatment of coronary narrowing implies radical restriction of the energy output; and of coronary occlusion, the liberal use of morphine and prolonged bed-rest to encourage collateral circulation.

Surgical measures offer relief in a limited number of patients with precordial pain for whom life is a burden or work impossible.

## THE CORONARY PROBLEM IN HEART DISEASE

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THE clinical recognition of coronary artery disease constitutes a new chapter in internal medicine, in the development of which American physicians have taken a prominent part.

As the clinical significance has come to be more generally recognized, a new impetus has been given to investigation of the anatomy, physiology, and pathology of the coronary circulation. The relation of myocardial infarction to clinical phenomena has been more firmly established, and a clearer conception of the distribution of cardiovascular pain, as well as the diagnostic significance of electrocardiographic changes, has greatly widened our knowledge of this problem.

These various studies and observations have gradually permitted the construction of a clinical picture of coronary artery disease which is one of the distinct contributions of modern internal medicine. This newer knowledge has, likewise, materially advanced our understanding of chronic heart disease, particularly as it pertains to the adult, and later periods of life.

*Anatomic and experimental studies.*—The blood supply to a tissue is often a key to the understanding of pathologic processes which may occur in the same, and the study of the coronary circulation has been further stimulated by the constant endeavor to correlate it with clinical phenomena incident to coronary artery disease.

For a long period, studies have been made to determine anastomosis between the branches of the coronary arteries, and with the arteries of surrounding structures. This has been quite definitely established by experimental ligation in animals, clinical observations with necropsy dissection, injection of the coronary arteries with subsequent corrosion of the extravascular tissues of both normal and diseased human hearts, and roentgenologic studies.

Cohnheim,<sup>1</sup> in 1881, was probably the first to apply the term "end arteries" to the coronary arteries, his conclusions being based on the experimental ligation of either coronary artery in curarized

dogs producing standstill of the heart in two minutes. These were modified by Porter,<sup>2</sup> who, in 1896, found that stoppage of the heart resulted in 88 per cent. after ligation of the circumflex, and in 64 per cent. after ligation of the descendens. Yet, by studying infarct formation after coronary ligation in dogs, he found that all the animals did not necessarily die. The reason for this was demonstrated by Spalteholz,<sup>3</sup> and by Hirsch,<sup>4</sup> who found after coronary ligation in dogs and monkeys that the region infarcted was always smaller than the region supplied by the ligated artery.

A subsequent study by Miller and Matthews<sup>5</sup> confirmed the work of Spalteholz, and determined that either main branch of the left coronary artery in the dog could be ligated without seriously disturbing the heart, but if the circumflex branch was previously ligated, a cardiac standstill resulted, the left ventricle stopping beating first. In their opinion, the premonitory evidence of cardiac standstill was arrhythmia, incomplete systole of the left ventricle, and gradual over-filling with dilatation of the left side of the heart, and later dilatation of the right auricle and ventricle.

The inadequacy of communicating branches in human hearts for purpose of complete anastomosis was recognized by Huber,<sup>6</sup> and Silverthorn<sup>7</sup> in the study of human hearts removed from the bodies of persons dying of coronary artery disease. Although collateral circulation existed between the coronary arteries and adjacent structures with acutely developing obstruction, the compensatory circulation may prove inadequate, or not be established promptly enough to prevent sudden death.

Galli<sup>8</sup> was the first to recognize that the gradualness of occlusion of a coronary artery was important for the development of an adequate collateral anastomosis because he found no gross or microscopic change of the myocardium following total occlusion of the mouth of the right coronary artery.

Merkel<sup>9</sup> also found no myocardial change following gradual occlusion of the left coronary. From these observations it would seem that an absence of myocardial change following occlusion of a coronary artery demands that the occlusion be brought about slowly.

Herrick<sup>10</sup> clinically arrived at the conclusion that the variation in anastomosis, the size of the vessel occluded, and the condition of

the remaining branches are all factors related to a failure for death to result abruptly with coronary artery thrombosis or embolism.

The comprehensive monograph of Gross,<sup>11</sup> in 1921, as well as that of Spalteholz,<sup>12</sup> in 1924, presents clearly the diffuse distribution of the coronary circulation, particularly the anatomy of the neuromuscular circulatory structure, and the blood supply of the heart valves and subendocardial tissues. While there is no sharp line of demarcation between the supply of the right and left coronary arteries, since their branches overlap, a profuse and abundant anastomosis leaves a wide border-line which is supplied by both vessels. Gross also came to the conclusion that the heart is abundantly provided with capillary and precapillary anastomoses which are normally not in use, so that they are inadequate for emergencies, but may become adequate with gradual obstruction.

Oberhelman and Le Count<sup>13</sup> maintain that some of the difficulty in understanding coronary disease of the human heart and its sequence is directly attributable to a general disposition to regard the coronary arteries, and their entire arterial bed as an anatomic "invariable," whereas such is not the case. Not only are there variations which are consistent with normal conditions, but a still greater variation is brought about by disease. These variations were well brought out by their examination of twenty-six human hearts, mostly from males between the ages of fifteen and seventy years. The hearts were injected with metallic mercury, under a pressure of from 125 to 150 millimeters, through a cannula tied into the mouth of one coronary artery, a number of injections being made under the fluoroscope. In one group of nine hearts there was no evidence of collateral anastomosis, myocardial disease or arterial change demonstrable, and both arteries had to be injected separately to fill the arterial system. In another group of five hearts there was no myocardial or arterial disease but they possessed definitely demonstrable anastomoses because the entire arterial system filled through the mouth of one artery. In a third group of four hearts, diseased arteries were present with definitely demonstrable collateral anastomoses. A final group of eight hearts with extensive myocardial changes, almost or total occlusion of one or another artery, had abundant demonstrable collateral circulation.

From these studies the authors conclude that there are two factors

connected with these "variables" of considerable importance as concerned with disease of the coronary arteries, and its sequences. One is the difference that the arterial bed of the myocardium may possess, normally, as to anastomoses between the branches of the two coronary arteries. The other is the time element, whether narrowing in the channels of the branches of either or both arteries, or total occlusion by any process whatsoever, occurs abruptly or slowly, for, with the more gradual occlusion, a marked compensatory anastomosis may be developed.

Barnes and Whitten<sup>14</sup> have added some interesting anatomic facts by demonstrating a difference between the right coronary supplying the right ventricle, and the branches of the right and left coronary arteries supplying the left ventricle. The branches which supply the left ventricle whether they originate from the right or the left coronary artery, course along the surface of the heart just beneath the epicardium. Their branches do not spread out in a general plane but instead they leave at right angles and penetrate straight through the myocardium, giving off very few branches until they reach the endocardium where they again turn at a sharp angle, and end in a mass of fine arterioles. By this anchoring of these branches it can readily be assumed that in hypertrophy of the left ventricle, the blood vessels become elongated and tortuous, and more readily lead to narrowing and occlusion of the lumen through endarteritic changes. It also suggests a reason why occlusion of the right coronary artery is manifested chiefly by infarction in the posterior portion of the left ventricle.

Wearn<sup>15</sup> has made a careful study of the capillaries of the normal average heart indicating a very rich blood supply with an average of approximately one capillary for each muscle fiber in the ventricular walls and papillary muscles and a less abundant supply in auricular muscle, and the Purkinje system. The number of capillaries per square millimeter of ventricular wall or papillary muscle is about twice that found by Krogh<sup>16</sup> in skeletal muscle.

The same author<sup>17</sup> has studied the rôle of the thebesian vessels in the circulation of the heart, and presents evidence that there is a direct connection through the thebesian veins, other than through the capillaries, between the coronary arteries and the chambers of the heart; furthermore, that capillaries drain directly into the thebesian

veins, and that under certain conditions as much as 90 per cent. of the arterial flow may escape via the thebesian vessels; lastly, in the event of gradual closure of the orifices of the coronary arteries, the thebesian vessels can supply the heart muscle with sufficient blood to enable it to maintain an efficient circulation.

Kugel<sup>18</sup> has contributed an interesting study made on fifty normal human hearts, and demonstrating a large anastomotic blood-vessel which runs in the auricular walls, and links up the left, and right coronary arteries. It also supplies branches to the aortic and mitral valves, the commissures, and base of the aorta. He corroborated an observation reported by Gross, that in several hearts which were the seat of arteriosclerotic disease, this large anastomosing artery was of usually large caliber. The distribution of this vessel has an important bearing in that it offers an explanation as one of the factors concerned in the localization of lesions in the commissures such as have been found in rheumatic disease, subacute bacterial endocarditis, and syphilis.

A considerable part of the information that has been developed on the blood supply of the heart is based on experimental investigations on dogs, with the assumption that changes in the coronary arteries in the dog and man must rest on a similar anatomic structure, origin, course, and distribution. It is, therefore, of interest to note the results of a recent study by Moore<sup>19</sup> in which it is determined that the coronary arteries of the dog differ from those of man in two major points: (a) the presence of a distinct and separate septal artery as a branch of the left coronary artery; and (b) the formation of the posterior descending artery by the left in all cases rather than in 20 per cent. in man. As the origin and course of the septal artery renders experimental ligation difficult, it seems improbable that previous investigators have been able to interrupt the blood supply to the septum, which fact gives to this investigation of Moore's a very important significance.

*Disease of the coronary arteries and sequelae.*—The coronary arteries are subject to various pathologic changes, as atheroma, atherosclerosis, syphilitic arteritis, and the different chronic endarteritides—all of which produce a gradual obstruction of the artery. Sudden occlusion is due to thrombosis, less often embolism.

Herrick and Smith<sup>20</sup> reported an acute arteritis and endarteritis caused by surgical tying-off the coronary artery.

Interference in the coronary circulation, partial or complete, has long been known to lead to pathologic changes, particularly infarction of the myocardium, and in some instances produced death.

The clinicians and pathologists of the first half of the nineteenth century regarded fatty degeneration as the end-result of coronary occlusion of which Richard Quain<sup>21</sup> was the best-known exponent.

It is to be regretted that Rokitsansky and Friedreich, with their unusual necropsy and clinical experience, missed the opportunity of studying the coronary arteries. Both believed fatty degeneration of the heart to be the most frequent cause of heart failure.

Pathologists of England and the Continent evidently witnessed myocardial infarcts, with and without rupture, but missed their true significance. If more heed had been given to the statement of Dr. Hilton Fagge, in 1874, that "this affection never attacks the whole heart at once, nor even the whole of a single chamber," the concept of infarction would have been more probable.

Benson<sup>22</sup> quotes an interesting observation of an obscure American physician, Winsor,<sup>23</sup> who, in 1880, described a case of angina pectoris with rupture saying, "In the vicinity of the rent, the characteristic appearance of the muscle was lost, the muscular fibers being here filled with a granular material, and in many places with minute fat drops. The walls of the left coronary artery were thickened and sclerotic and their lining covered with yellowish-white patches. At one point, about three centimeters from the origin of the artery, one of these patches had so far protruded into the lumen of the vessel as to cause a coagulation of blood at that point, which coagulation had become adherent to the walls, thereby preventing the flow of blood through the vessel. The portion of the heart in which the rupture had occurred, and in which the fibers were found degenerated, corresponded to the territory supplied by the branches of this artery."

Weigert,<sup>24</sup> in 1880, was the first to expound the doctrine of cardiac infarction, and he definitely established the complete analogy between coronary infarction and the same process in other organs.

In the same year, 1880, Ziegler<sup>25</sup> introduced the term "myomalacia cordis," but his definition was not as convincing as the descriptions of Weigert and Winsor. Yet, in his *Lehrbuch*, 1887, Ziegler<sup>25</sup>



FIG. 1.



Mrs. M., 58 years, periodic attack of digestive distress with epigastric pain for five years.  
Autopsy: Atheromatous aorta, large fibrous infarction scar, left ventricle.



gives a description of the types and results of coronary obstruction which, with minor changes, corresponds to our conception of today.

Ziegler also regarded myomalacia cordis, not aneurysm, the direct precursor of rupture, and amended Weigert's teaching that all scarring of the heart results from anemic necrosis of muscle with the wise reservation that a part of it is due to inflammation. This interrelation of coronary occlusion and myocardial ischio-necrosis has been supported by numerous pathologic and clinical reports which have since appeared and continue to abound in medical literature.

The experimental obstruction of the coronary arteries as carried out in the investigations of Miller and Matthews,<sup>5</sup> Karsner and Dewyer,<sup>27</sup> Smith,<sup>28</sup> Wearn,<sup>17</sup> and others, developed definite infarction similar to those observed in human hearts. The extent of the infarction varies from very small (almost microscopic) areas of necrosis and fibrosis to those involving a large portion of the ventricular wall. The location varies, likewise, from near the endocardial, or pericardial surface, to all portions of the ventricular musculature. The apex is a frequent site, and the left ventricle is involved oftener than the right.

In the accompanying illustration, Fig. 1, is shown a large wedge-shaped infarction scar found at autopsy in a patient with a history of recurrent angina attacks extending over a period of five years.

The macroscopic picture of myomalacia cordis, or fibrous myocarditis, represents a series of small infarctions replaced by fibrosis, which gradually produces dilatation and myocardial failure. The thinning of the ventricular wall by a large acute infarction leads readily to aneurysm and rupture.

That these sequelae do not always follow narrowing or occlusion of the coronary artery has been previously explained as due to variations in the coronary circulation, and anastomoses. Of the various opinions expressed regarding the pathology of coronary artery disease, that of Le Count,<sup>29</sup> in 1918, still seems most logical, "that somewhere between sudden occlusion and its results, and such slowly developing obstruction that few or no symptoms develop, lie the lesions responsible for angina pectoris." Nevertheless, with such a pathologic background of myocardial infarction, it is possible to correlate some of the characteristic clinical phenomena incident to coronary occlusion. A large infarction suddenly produced readily explains the

various phenomena of shock, the sudden drop in blood-pressure, muffled heart sounds, and relaxed peripheral circulation, followed later by leukocytosis and fever. If the infarction area can heal by replacement fibrosis, a fair degree of cardio-circulatory balance can be maintained for years as borne out by subsequent clinical observation.

*Coronary occlusion—a clinical entity.*—Until within the last two decades the concept of coronary occlusion and cardiac infarction as a clinical entity was called among the rarities in medicine. Only recently has it received its proper recognition in text-books and systems of medicine. It is interesting to recall that the eminent English physician, Sir William H. Broadbent,<sup>30</sup> in his monograph on Heart Disease, 1906, states "there are no characteristic physical signs or symptoms by which thrombosis of the coronary arteries can be diagnosed." Yet, in this country, Dock<sup>31</sup> was one of the first to emphasize the probability of diagnosing the condition before death, and in 1896 he lamented the fact that the profession was so slow in taking up the study of the disease. He also observed that "a heart, although extensively necrosed, may continue to act for some time fairly well," and he was among the first to recognize the true relationship of pericarditis to the syndrome.

We are indebted to Osler,<sup>32</sup> for the first real correlation of the clinical and pathologic findings as presented in the Lumleian Lectures in 1910 on the subject of angina pectoris.

Considering angina pectoris as a disease entity, he discusses in his peculiarly attractive manner the incidence, etiology, pathology and clinical records that strike a familiar note in comparison with the descriptions of coronary occlusion of this later period. He refers to angina pectoris as "a disease characterized by paroxysmal attacks of pain, pectoral or extra-pectoral, associated with changes in the arterial walls, organic or functional." He evidently regarded it primarily as an affection of the arterial system which he aptly terms "the pump and the pipes" of the system in which "are literally the issues of Life and Death." He maintained that its protean features can not be understood unless it is remembered that the arteries are only a long-drawn-out extension of the heart, and the heart but a bulbous expansion of an artery.

Osler evidently felt that angina pectoris was on the increase, and

considered the high-pressure life of modern days as a probable factor. Also, that it was seen more frequently in private practice than in the hospital ward, which appeared to support the familiar conception that angina pectoris was an affection of the better classes. In presenting personal statistics of angina pectoris, the incidence of sex and age compares closely with the tables of Levine<sup>33</sup> on coronary thrombosis. One-eighth of Osler's cases<sup>32</sup> were in physicians, and he felt that angina might well be called "*morbus medicarum*." Curtin,<sup>34</sup> in a previous study of sixty fatal cases of angina pectoris in the United States, had found that a fourth were among physicians.

It was but natural for Osler to refer to the long list of distinguished physicians who had been victims of angina pectoris and to make special reference to the great Vienna clinician, Nothnagel, whose last act in life was to describe his own fatal attack. In a note written a few hours before the end came, appear these words: "Anginal attacks with very severe pains; pulse is in the attack very variable, at one time slow, 56 to 60, quite regular, high tension, and then again rapid, 80 to 90, tolerably even and regular; then again quite unrhythmic, unequal at one time, rapid another, low with changed tension. The first sensation of this attack dates three to four years back, at first slight, gradually becoming more pronounced. Very severe attacks with great pain have only come on within the last five or six days. Written on July 6th, late in the evening, after three very severe attacks." This description fits in with the symptoms of acute coronary occlusion and cardiac infarction as recognized today.

Osler recalls also the late William Pepper, who died "with coronary arteries like pipe stems," referring to him as "the most brilliant and devoted physician of his generation in the United States." "The Provost, indeed the maker of a great University, the very head and front of every important public movement in a city of a million inhabitants, a universally sought consultant, an enthusiastic teacher, a prolific author, in him was incarnate the restless American spirit which drove him into a premature grave at the height of his career at the comparatively early age of fifty-five."

Osler classified angina pectoris into three clinical types of very mild, mild, and severe forms, subdividing the latter into:

- (a) Cases in which death occurred in the first or second attacks,

or in connection with a series of rapidly recurring attacks—the so-called status anginosus;

(b) Cases in which the patients have had a series of characteristic attacks ranging from two to three to scores during the course of a few months or a year or more, with death occurring in a severe paroxysm, and:

(c) A chronic form, which is characterized by frequent recurring attacks over a period of more than ten years. The case of John Hunter is cited, who had his first seizure in 1773, twenty years before his death, and he had many in the interval.

The two special features of the severe type of angina required by Osler were the existence in a large proportion of all cases of organic changes in the arteries and the liability to sudden death. This classification by Osler of angina pectoris bears a strong resemblance to that proposed by Herrick<sup>35</sup> for the different types of coronary occlusion.

Two theories prevailed among these earlier clinicians regarding the nature of angina pectoris. While Osler and an increasing number of physicians in America were adherents of the coronary artery theory prevailing since the time of Jenner and Parry,<sup>36</sup> Allbutt,<sup>37</sup> Wenckebach,<sup>38</sup> Vasquez,<sup>39</sup> Mackenzie,<sup>40</sup> and others, always contended that angina was due to the stretching of the wall of the aorta. Nevertheless, many of Allbutt's descriptions of the different forms of angina pectoris with clinical records and autopsy findings are typical of the present-day conception of coronary disease.

In this retrospective study it becomes evident that what we now recognize as cases of acute coronary thrombosis were formerly regarded as instances of severe angina pectoris, or status anginosus. Furthermore, the chronic form of severe angina described by Osler with frequent recurring attacks over a period of years, can well be compared to the gradual narrowing of the coronary arteries by endarteritic changes producing finally complete occlusion.

The distinction between angina pectoris and coronary thrombosis is only of recent development. The same year that the Lumleian Lectures on angina pectoris were given by Osler was marked by the first important publication of the clinical features of coronary thrombosis by Obratzow and Straschesko.<sup>41</sup> Two of these three cases were correctly diagnosed by these Russian observers. All three cases had precedent angina pectoris. They called attention to most of the

clinical features now recognized as important symptoms in coronary thrombosis. The following year, Hochhaus<sup>42</sup> published, without attracting any special attention abroad, a similar report of four cases, two of which were diagnosed *ante mortem*.

In 1912, Herrick<sup>10</sup> published his first interesting article in which he emphasized the fact that coronary thrombosis was a clinical entity, could be recognized during life, and that it need not end fatally. His careful observations and persistent efforts have done much to focus the attention of the American medical profession on this disease. Since then have appeared further reports by Herrick,<sup>35</sup> as well as those of Pardee,<sup>43</sup> Paullin,<sup>44</sup> Longcope,<sup>45</sup> Wearn,<sup>46</sup> Willius and Brown,<sup>47</sup> Gordinier,<sup>48</sup> Christian,<sup>49</sup> Scott,<sup>50</sup> and Conner and Holt,<sup>51</sup> indicating that it cannot be classed as a rare disease in this country.

Herrick, in 1919, proposed a very appropriate classification of the clinical forms under the following four types:

(1) Cases of instantaneous death in which there is no death struggle, the heart beat and breathing stopping at once.

(2) Cases of death within a few minutes, or a few hours after the obstruction. These are the cases that are found dead, or clearly in the death agony by the physician who is hastily summoned, and both forms are often first seen by the coroner.

(3) Cases of severity in which, however, death is delayed for several hours, days, or months, or recovery occurs.

(4) A group that may be assumed to exist embracing cases with mild symptoms: for example, a slight precordial pain ordinarily not recognized, due to obstruction in the smaller branches of the arteries. This type also resembles the chronic form described by Osler as a subdivision of severe angina.

The third type probably represents the form for which a typical clinical syndrome has been established, and is now readily recognized. The clinical phenomena are subject to considerable variation, depending in a large measure on the extent of myocardial damage.

Acute coronary occlusion is attended by two definite clinical manifestations, *viz.*, severe angina or status anginosus, and the symptoms of shock and collapse, with the attending phenomena of pericardial friction, leukocytosis, fever, and different forms of congestive heart failure.

*Distribution of cardiovascular pain.*—The time has not arrived for a definite opinion as to the origin and nature of the pain in angina pectoris. As stated by the physiologist Wiggers,<sup>57</sup> "An intelligent discussion of cardiac pain is not at present possible, for ideas as to the ultimate mechanisms producing pain remain wholly speculative."

In regard to the two theories that have prevailed for several decades, the aortic and the coronary, it appears now that an increasing number of clinicians are becoming adherents of the coronary artery theory. The observations made in connection with acute occlusion of the coronary artery have tended to strengthen the view that the paroxysm of angina of effort has its origin in a perversion of function of the coronary artery or the muscle supplied by that artery or of both.

In view of the dictum expressed by the eminent physiologist, there is a natural hesitancy in approaching the subject of cardiac pain, but the study of visceral reflex pain offers some interesting suggestions, and we venture to submit it.

Assuming that the origin of pain is connected with the heart muscle, the nerve supply of the heart and its coverings as related to that of other viscera and adjacent tissues become an important factor in understanding the distribution of cardiovascular pain.

The pain associated with coronary disease has the same characters as those which feature the reflex pains of visceral disease. While apparently having no affinity, the painful phenomena occurring in different diseased viscera present a well-defined similarity.

Although the heart, digestive tube, uterus, and ureter are fundamentally the same, and reflex symptoms such as pain are of like nature, the studies of Mackenzie,<sup>58</sup> Head,<sup>59</sup> and Sherrington,<sup>60</sup> indicate that the viscera are insensitive to the ordinary stimuli, that the organs and tissues supplied by the autonomic (sympathetic) nervous systems are not endowed with sensation in the same sense that it is used in regard to tissues supplied by the cerebrospinal nerves.

Head<sup>59</sup> summarizes referred pain from the viscera in these four statements:

- (1) It is often remote from the site of the irritation.
- (2) It follows lines on the skin of the spinal segmentation rather than the course of the peripheral nerves.



(3) It is usually associated with cutaneous hyperesthesia, and tenderness to pressure.

(4) Often the pain fails to involve the whole segmental area of the skin, but finds expression in one or more points of maximal tenderness and spontaneous pain.

FIG. 2.

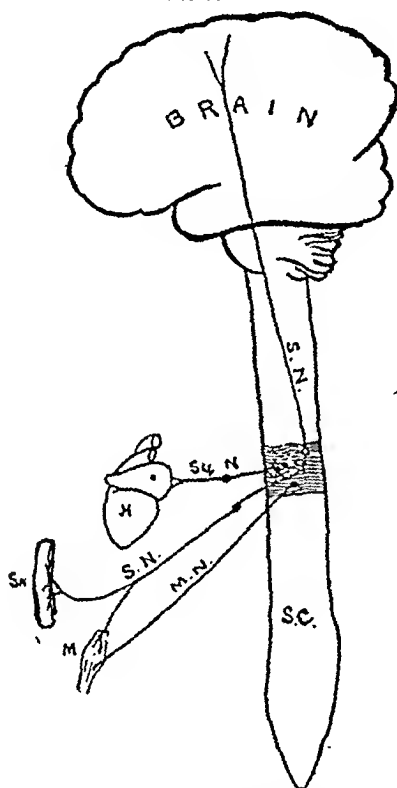


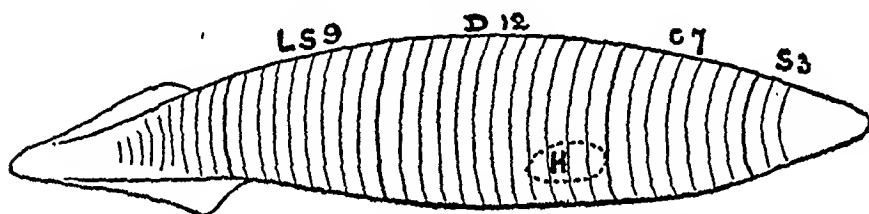
Diagram showing the mechanism producing visceral pain (adopted after Mackenzie and Head).

Therefore, a painful stimulus arising in the heart (H., Fig. 2) is conveyed by the sympathetic nerve (Sy. N.) to the spinal cord (S. C.). On reaching the cord the abnormal stimulus spreads beyond the sympathetic center and affects nerve-cells in its immediate neighborhood. The cells so stimulated react according to their function, the sensory causing a sensation which the brain recognizes as pain, and refers to the peripheral distribution of the sensory nerve (S. N.) in the skin or muscles, the motor (M. N.) producing contraction of the muscle (M). The pain and feeling of constriction about

the chest in angina pectoris and coronary occlusion can be explained in this way.

In order to appreciate further the mechanism of pain felt in affections of the heart, the manner in which the upper dorsal nerves come to be distributed are to be borne in mind. Ross<sup>61</sup> has pointed out that in the primitive vertebrates, before the development of the limbs, each spinal nerve is distributed segmentally round one-half of the body, Fig. 3. The upper dorsal nerves are therefore entirely distributed over the body-wall and to the tissues covering the heart. The upper limbs as they bud out from the trunk in their development drag with them away from the trunk portions of the cervical and upper dorsal nerves, so that parts of the first and second dorsal nerves

FIG. 3.



Diagrammatic representation of a primitive vertebrate animal to show the distribution of the sensory nerves. For clearness of comparison the number of segments is represented to be the same as in man, and the heart occupies the same position. Each nerve is shown as limited in its distribution to one segment (after Ross).

are distributed to the ulnar border of the forearm and inner surface of the upper arm.

Thus a painful stimulus arising in the heart and affecting the cord area of the first and second dorsal nerves would be felt as pain in the lower vertebrate over the heart, whereas in man it would be felt in the upper arm or in the forearm.

Aside from the reflex pains connected with the sympathetic nerve supply, the vagal sensory reflex is involved through stimulation of the vagus. As its center in the medulla is in near relationship to the upper cervical nerves, particularly to the nerves supplying the sternocleidomastoid and trapezius muscles, these muscles often become extremely hyperalgesic in various heart affections, but the pain may also be felt in the further distribution of the cervical nerves.

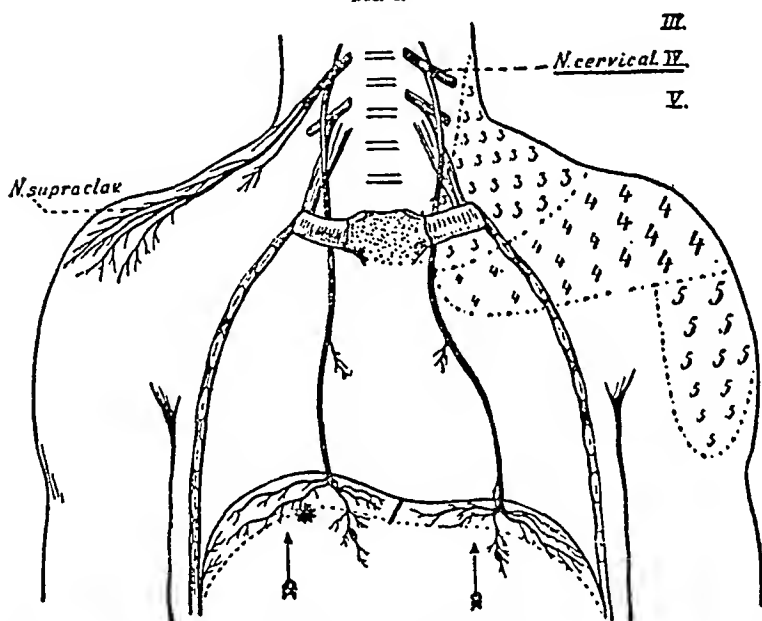
Due to the radiation of the stimulus from the vagus to the center of the fifth nerve, pain may be felt in the gums and throat during an attack of angina pectoris.

As a result of reflex stimulation of the floor of the fourth ven-

tricle, an abundant flow of saliva, and the secretion of large quantities of pale urine may occur. There are also good reasons for attributing some forms of dyspnea, and possibly nausea and vomiting to reflex stimulation from the heart.

A further interesting explanation of visceral pain is offered by the study of the development of the diaphragm and accompanying distribution of the phrenic nerve (Fig. 4).

FIG. 4.



Origin and distribution of phrenic nerve. Schematic illustration of spontaneous shoulder pain as referred symptom of phrenic irritation in disease of the upper abdomen and subphrenic area (after Oehlecker).

According to Mall<sup>62</sup> the anlage of the diaphragm lies in the head region of the early embryo together with those of the heart and liver as well as the three embryonic body cavities, the pericardium, pleurae, and peritoneum, which descend to their anatomic position during the process of development.

It will be noted that the diaphragm wanders from the head region to the abdomen passing by, as well as modifying structures and organs along the way.

The phrenic nerve arises in the cervical region in close connection with the third, fourth, and fifth cervical nerve roots, and enters the anlage of the diaphragm. As this organ descends, the phrenic

nerve lengthens to give it innervation, and is distributed during its downward course of the pericardium and covering tissues of the heart, the upper and lower surfaces of the diaphragm, the upper epigastrium, suspensory ligament and surface of the liver, and suprarenal capsule region. It also communicates with the diaphragmatic plexus as well as the semilunar ganglion of the solar plexus.

Very suggestive in this connection is the interesting publication of Oehlecker<sup>63</sup> on spontaneous shoulder pain in connection with inflammatory conditions of the upper abdomen involving the diaphragm; and that of Capps<sup>64</sup> on experimental study of the pain sense in the pleural membranes.

A clinical study of phrenic shoulder pain by Zachary Cope<sup>64</sup> and the importance of phrenic shoulder pain in disease involving the diaphragm by Orr<sup>65</sup> are all interesting contributions to the subject.

As left shoulder pain occurs in abdominal diseases involving the diaphragm and phrenic nerve, so also may pain arising in the heart area be referred to the epigastrium and upper abdomen. With the above in mind the diagnostic interpretation of referred pain in angina pectoris and coronary occlusion is given a more logical explanation.

*Electrocardiography.*—By furnishing certain graphic demonstrations of coronary disease and its effects on cardiac structure, the electrocardiograph has added valuable diagnostic information. As confirmatory evidence to be correlated with clinical findings it has proved of greatest value.

The electrocardiographic changes produced by coronary occlusion and cardiac infarction have been widely studied during the past thirteen years, and the clinical recognition has been greatly advanced by American internists who recognized that certain electrocardiographic changes were characteristic following acute coronary obstruction. The changes in the electrocardiogram are largely concerned with the end or ventricular phase—the Q.R.S. complex and the T wave.

Lewis, in 1910, published the result of ligation of the coronary arteries in animals in which disturbances in heart rhythm were produced and which are similar to changes in rhythm now known to follow coronary thrombosis in man.

The classic experiments of F. M. Smith<sup>28</sup> published in 1918 furnished the first definite evidence that ligation of the left coronary artery in the dog produced myocardial lesions and a resulting nega-

tive T wave in one or more leads of the electrocardiograms. These observations were further confirmed by a later publication in 1920, reporting the results of ligating various branches of the ramus descendens and circumflex sinistra. Of the twenty dogs used in the experiments, sixteen survived the operation, and of these fourteen showed a negative T wave following the ligation. It is interesting to note that the various phases of T wave negativity produced by ligation of the coronary arteries in animals have been fully confirmed by more recent clinical observations, particularly where a series of electrocardiograms have been made at frequent intervals following acute coronary occlusion.

Herrick<sup>35</sup> in 1919, published an account of coronary thrombosis proved by postmortem examination in which electrocardiograms had been made showing a sharp inversion of T waves in leads one and two.

In 1920, Pardee<sup>43</sup> reported an electrocardiographic sign of coronary artery obstruction which he regarded as having diagnostic significance. This sign consists of a particular deformity of the R. T. segment in which there is a sharp take-off from the descending limb of the R wave followed directly by a sharp inverted T wave—thus obliterating the usual R. T. or S. T. iso-electric interval. This was present in one-third of his patients who gave symptoms of coronary narrowing or infarction. Pardee hoped thus to show that obstruction of the branch of the coronary artery is followed by a sign which is characteristic of this condition.

This, to a large extent, has been confirmed by the observations of Herrick, Smith, Willius,<sup>67</sup> Wearn, Levine, White,<sup>68</sup> Wiggers,<sup>69</sup> Barnes and Whitten,<sup>70</sup> Stewart,<sup>71</sup> and particularly by the serial records published by Parkinson and Bedford,<sup>73</sup> and more recently by Cooksey and Freund.<sup>74</sup>

This apparent constancy of T wave changes following coronary occlusion and cardiac infarction appears to uphold the idea first expressed by Pardee that when muscular tissue of the heart is diseased there will follow abnormal variations in electrical currents due to the heart's contraction.

Bates and Talley<sup>72</sup> have reported a case of a young man who had a stab wound in the base of the left ventricle, in the region of the main branches of the left coronary artery. The wound was closed surgically, and he made a complete recovery. The first electro-

cardiogram, taken five days after the injury, was that of acute coronary occlusion. The second curve, taken twelve days after the injury, was intermediate between the acute and chronic coronary occlusion. Twenty days after the injury, T-1 and T-2 showed the typical inverted T wave and circumflex upward R. T. interval of chronic coronary occlusion, which reached its maximum twenty-six days after the injury. After this time the inverted T-1 and T-2 began to recede and had the normal upright T on March 27, 1929—that is, eighteen weeks after the wound and operation.

In the serial study of electrocardiograms made by Parkinson and Bedford<sup>73</sup> in twenty-eight patients after acute coronary occlusion covering periods of many months—one case, nine and one-half years—emphasis is placed upon a primary or initial deviation downward or upward from the iso-electric line of the R. T. curve. This deviation was noted by Smith in electrocardiograms taken after ligation of the left coronary artery in dogs. This initial deviation as a rule gradually disappears and is usually followed by the Pardee negative T wave which remains for varying periods of time.

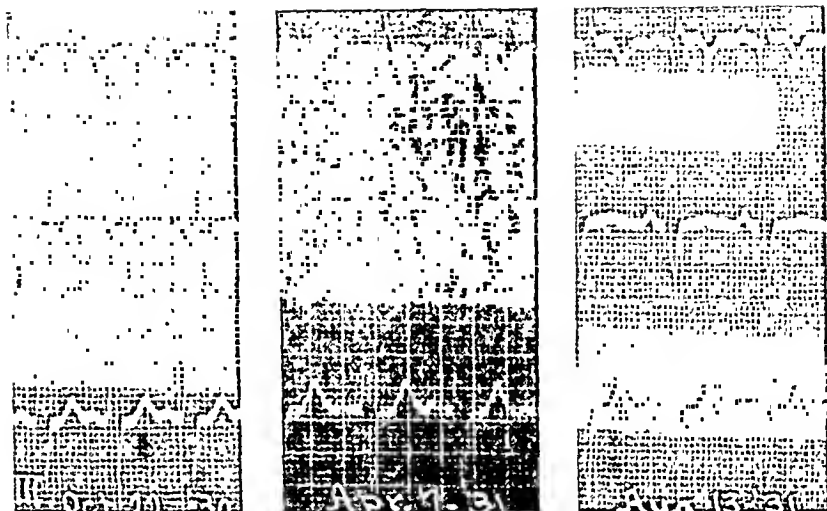
In the publication of Cooksey and Freund,<sup>74</sup> comprising a serial study of electrocardiograms observed in twenty-four patients following acute coronary occlusion, the Pardee curve entirely disappeared in four cases at periods of six, ten, twelve, and fourteen months, while in four cases the Pardee negative T wave was present at the end of eighteen, twenty, twenty-four, and thirty months.

Fig. 5 shows three electrocardiograms taken within one year after acute coronary thrombosis in which the Pardee R-T curve and negative T wave persists in Lead I. Fig. 6 presents a negative T wave in all three leads 32 months after an attack of acute occlusion.

The negative T wave may be regarded as a fairly constant sign of previous coronary occlusion and cardiac infarction. It, therefore, seems reasonable to assume that obstruction of the coronaries may develop gradually by the narrowing of the lumen of a vessel from arteriosclerosis, and lead to a similar area of degenerative muscle as is found some time after acute occlusion by a thrombus, and that such a condition can present the negative T wave and other recognized electrocardiographic signs.

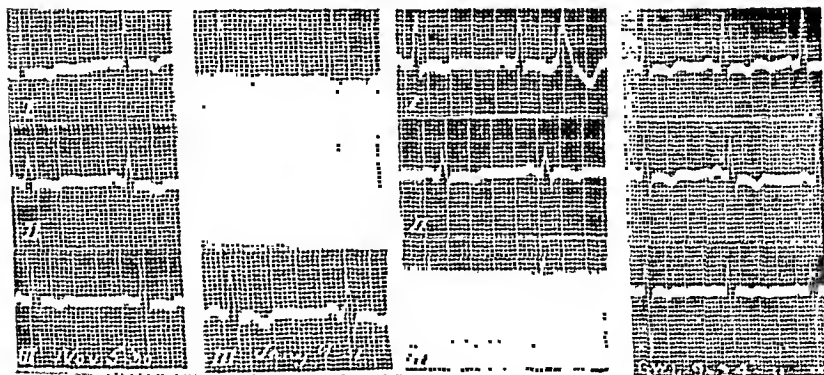
Figs. 7 and 8 represent significant electrocardiograms of two patients with a history of attacks of cardiac failure, angina pectoris,

Fig. 5.



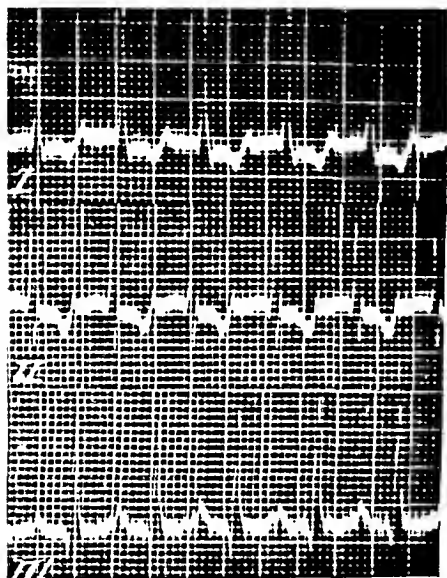
Mr. H., 49 years, acute coronary thrombosis September 9, 1930, Pardee "R T" curve and negative "T" wave persists for 11 mos. in Lead I. Left axis deviation.

Fig. 6.



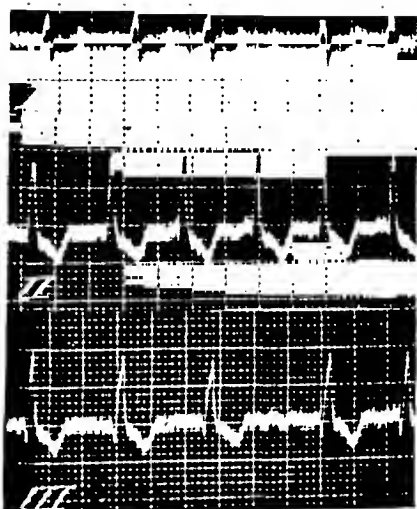
Mr. L., 79 years, acute coronary occlusion January, 1929, persistent negative "T" wave in all three leads for two years. Left axis deviation. Occasional extra-ventricular systole.

FIG. 7.



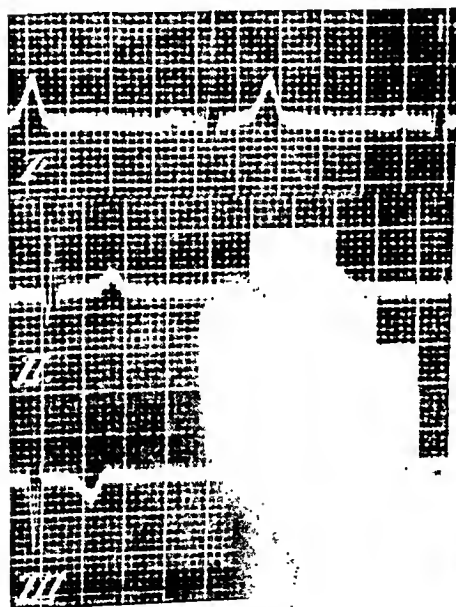
Mrs. M., 76 years, anginoid syndrome and persistent tachycardia for 5 years. T1, T2, negative, Ventricular tachycardia.

FIG. 8.



Miss L., 61 years, acute coronary occlusion in 1928. Auric fibrillation T1, T2, and T3, negative.

FIG. 9.



Mr. H. H. B., 70 years, complete A-V and bundle branch block.

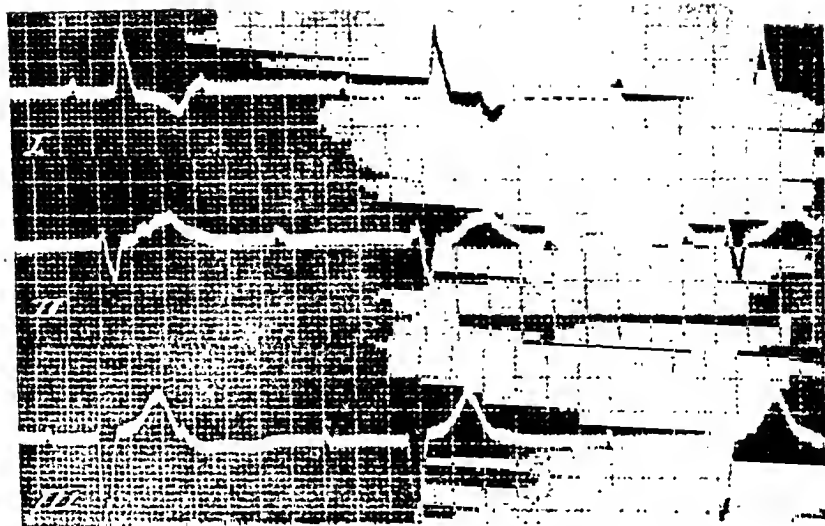
FIG. 10.



Mrs. A. B.  
axis deviation

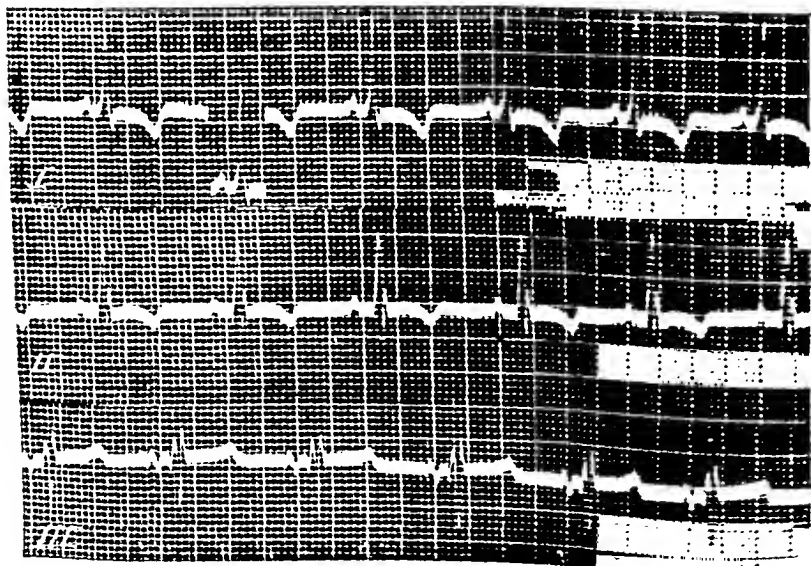


FIG. 11.



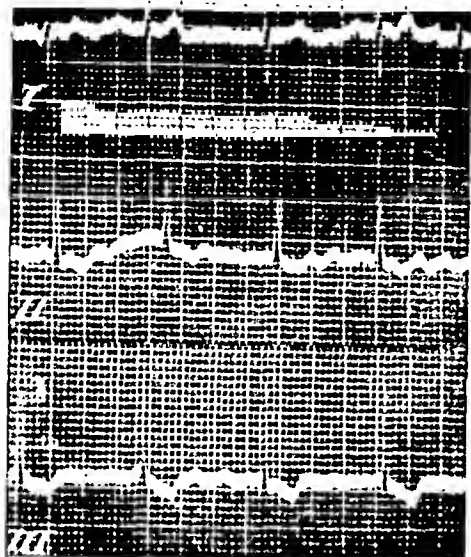
Mr. P., 73 years, T1 inverted. A-V complete right bundle branch block. Left axis deviation. P-R interval prolonged.

FIG. 12.



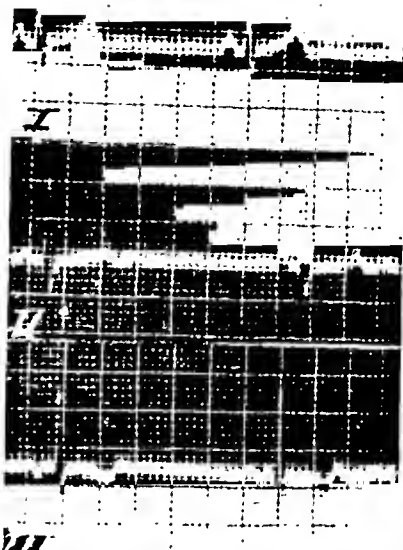
Mr. P., 43 years, T1, T2, inverted. Q.R.S. 2 & 3 complex abnormal. Left axis deviation.

FIG. 13.



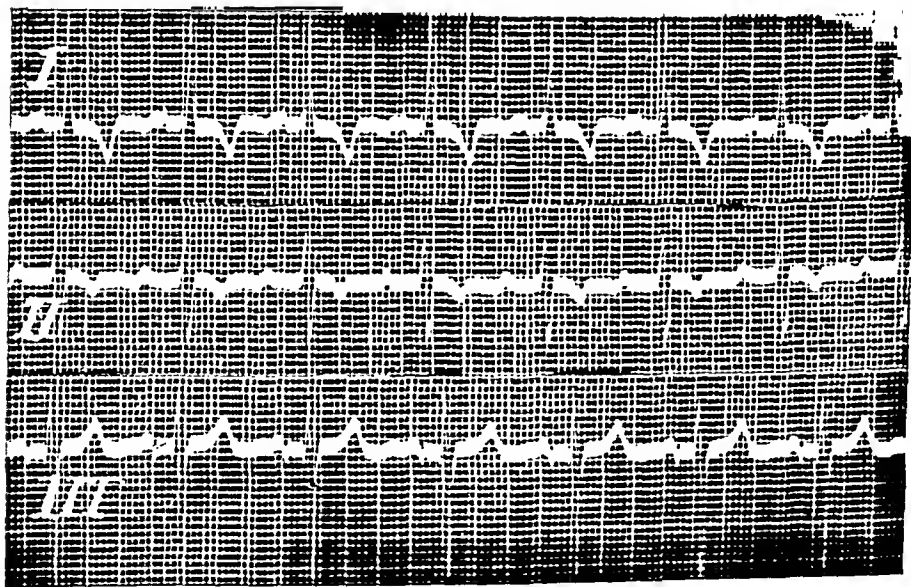
Miss P., 19 years, rheumatic heart disease. Digitalis administration 16 months. Sharp inversion of T2 & T3.

FIG. 14.



Mr. McN., 17 years, chronic infective tonsillitis. T3 inverted. Sinus bradycardia.

FIG. 15.



Mr. M., 26 years, rheumatic heart disease. Aortic insufficiency. L.V.P. T1, T2 negative.

and tachycardia covering a period of four years, and other symptoms of coronary artery disease.

As Willius states, the almost constant occurrence of T wave negativity in coronary thrombosis is the most important evidence that links this characteristic with obliterative coronary disease.

Changes in the Q.R.S. complex of the electrocardiograms, as to amplitude, slurring and widening as signs of coronary occlusion and myocardial infarction have been emphasized by Willius, Pardee, Wearn, Barnes and Whitten, Levine, as well as the serial studies of Parkinson and Bedford and Cooksey and Freund.

Low amplitude, flattening and sudden falls in amplitude of the Q.R.S. complex are recognized as signs of a bad prognosis when it occurs in the wake of an acute coronary occlusion. Complete or incomplete bundle-branch block, while infrequent, is met with in cardiac infarction. The signs of left ventricular preponderance or left axis deviation are frequently noted. Complete heart block is very infrequent as only in rare instances is the interventricular septum involved in infarction.

Figs. 9 and 10 illustrate electrocardiograms with negative T wave in Lead III, and signs of A-V and bundle-branch block from two patients in which the principal clinical symptoms were a slow pulse and occasional fainting attacks with substernal pain upon exertion.

Fig. 11 represents an electrocardiogram showing negative T wave in Lead I and abnormal Q.R.S. complexes in all three leads. A-V and also bundle-branch block are shown. These are from a patient, Mr. P., seventy-three years of age, whose only subjective discomfort is exhaustion, and consciousness of a slow pulse.

These different observations indicate that the changes in the Q.R.S. complex and T wave can show great variations during the different stages of coronary artery disease.

Pardee<sup>75</sup> has recently directed attention to the occurrence of a large Q wave in Lead III, the records being obtained from patients with the anginal syndrome. In certain patients with congestive heart failure, rheumatic heart disease and a few instances with normal hearts have also shown this phenomenon. Willius<sup>83</sup> has since reported a study of 300 cases in which there are electrocardiograms with large Q waves in lead 3, according to the criteria of Pardee. Only three cases (one per cent.) were noted in which the patients

apparently had normal hearts were found. The remainder had one of the following conditions: hypertensive heart disease, arteriosclerotic heart disease, with or without the anginal syndrome, or other diseases that exert their influence chiefly on the left ventricle. In 198 cases (66 percent of 300) the large Q wave in lead 3, was the only significant electrocardiographic feature present, permitting the conclusion that this abnormality may be considered as an additional diagnostic sign.

The occasional failure to obtain characteristic electrocardiograms in definite clinical cases of acute and chronic coronary occlusion has led some clinicians to question their diagnostic significance.

As further records are presented of electrocardiograms taken at frequent intervals, the constancy of characteristic changes will be more generally recognized. On the other hand, the electrocardiogram will occasionally reveal changes indicative of coronary artery disease where the principal clinical signs are lacking.

Fig. 12 illustrates such an instance in a man forty-three years of age with marked peripheral arteriosclerosis, but no other definite signs of cardiovascular disease. He did, however, become easily exhausted with exertion, had a moderate anemia of the type and was losing weight. The electrocardiogram suggests rather marked coronary artery disease.

The occurrence of a negative T wave or R-T deviation in other conditions has also led to some confusion. Porte and Pardee,<sup>76</sup> and Scott, Feil and Katz,<sup>77</sup> have reported the coronary T wave and R-T deviation similar to those seen in recent myocardial infarction in rheumatic pericarditis and in acute pericardial effusion.

Fig. 14 represents an electrocardiogram of a young man seventeen years of age with chronic infectious tonsillitis showing a negative T wave in Lead III, a slurred Q.R.S. complex in Lead I, and sinus bradycardia.

Fig. 15 shows an electrocardiogram of a patient 26 years of age with rheumatic heart disease, aortic insufficiency and cardiac hypertrophy. The T wave negativity is very suggestive of coronary artery disease.

The effect of digitalis on the electrocardiogram has been studied by Cohn,<sup>78</sup> White,<sup>79</sup> and others. Digitalis may cause marked inversion of the S-T interval, the shape of this interval and of the T wave being so characteristic that a glance at the electrocardiogram may

sometimes suffice for the diagnosis of a marked digitalis effect. (Fig. 13.)

Careful records, frequent observations in each case, and constant correlation with clinical phenomena will establish electrocardiography as a helpful adjunct in the diagnosis of coronary artery disease.

*Treatment.*—The new conception of coronary artery disease has influenced the therapy of the condition to a considerable extent. The outstanding symptom in acute or chronic coronary disease is pain, and there is a general recognition of the debt of Lauder Brunton for his discovery in 1867 of the nitrites in the treatment of angina. While in no sense curative, the vasodilation produced has a distinctly soothing effect and is a boon to the sufferer with periodic angina.

A different consideration must be given to the prolonged angina or status anginosus incident to acute coronary occlusion with the accompanying signs of shock and collapse as indicated by the sharp fall in blood-pressure, the cold clammy skin, and extreme exhaustion. At this time the vasorelaxant remedies have no therapeutic purpose.

The severe and oftentimes excruciating pain of status anginosus requires the hypodermic use of morphine in one-half-grain doses, and it may be necessary to repeat this dose once or twice before relief is obtained. This relief of pain is very necessary in order to properly carry out the next important essential, that of rest, which should be as complete as possible.

Special nursing is necessary, and the patient should not feed himself for several days. Exertion incident to the use of the bed pan should be guarded most carefully, as it has happened that a patient in attempting to go to the toilet has died during the effort.

The application of digitalis is dependent upon the development of signs of myocardial failure such as dilatation, pulmonary edema, or further indications of visceral congestion. There are occasions soon after the onset of the coronary occlusion that judicious use of digitalis has given most striking results.

After the acute symptoms of occlusion apparently subside, further indications of cardiac failure with visceral congestion may develop for which again the use of digitalis and other appropriate measures are indicated.

The management after the patient is allowed out of bed is de-

serving of careful supervision. Graded exercises have an important function at this stage, and all activities should be carefully regulated, so as not to extend to the point of shortness of breath.

In conditions of well-established coronary disease as indicated by recurrent attacks of exhaustion, dyspnea, angina with effort, and characteristic electrocardiographic changes, a distinct advance has been made in the better appreciation of the pharmacologic effect of certain drugs that promote an increased coronary flow.

The experimental ligation of the coronary arteries in dogs by Smith and others, as well as the observations on man following occlusions of these vessels, has demonstrated that the heart is extremely sensitive to the reduction of its blood supply. It is further recognized that a knowledge of the factors concerned in the regulation of the coronary circulation has an important bearing on a better understanding of impaired cardiac function.

In this connection the action of the vagi and the sympathetics has been more extensively investigated than any other physiologic aspect of the coronary circulation.

The experiments of Smith and his co-workers<sup>81</sup> indicate that the rate of coronary flow is greatly altered by the change in diastolic pressure, and the maintenance of an efficient coronary circulation is fundamentally dependent on the height of the diastolic pressure. Drugs which promote a greater coronary outflow appear to increase diastolic pressure.

By perfusion experiments, Guggenheimer and Sassa<sup>80</sup> have found that the action of drugs like caffein, theobromin, and theophyllin, on the isolated heart of a cat produces an increase in coronary outflow in the following proportions:—With caffein in dilutions of 1 to 25000, and 1 to 50000, there resulted an increase in rate of coronary flow of 41 per cent., and with theobromin and euphyllin of similar dilution an increased rate of 40 to 80 per cent.

Smith and his associates in their experiments have been concerned mostly with theophyllin and its derivative euphyllin, the former in dilutions of 1 to 25000 and 1 to 50000, promoting an increased rate of flow of 25 to 45 per cent., while the latter preparation increased the rate of perfusion from 40 to 90 per cent.

This experimental work has formed a logical basis for the therapeutic use of these preparations in the human person affected with coronary artery disease.

Euphyllin or metaphyllin, as well as amidophyllin, is administered in doses of one and one-half to three grains three times daily, and may be used over a long period of time; a personal observation of its use in one patient for two and a half years did not show any undesirable effects.

Theobromin may be employed and recently theocalcine has been highly recommended.

The manner of the diuretic action of these drugs is still undetermined. To what extent they promote an increased rate of coronary flow is also difficult to determine clinically. After their use in a considerable number of cases, the impression is gained that the angina and other cardiac discomfort is distinctly relieved. No doubt the elements of rest and restriction of activities are also factors to be considered. A sedative as pheno-barbital is often of benefit. For recurrent angina pectoris where the patient is confined to bed, the administration of nitroglycerine, as suggested by White, taken four or five minutes before some necessary effort has distinct prophylactic effect.

In recent years various surgical and injection procedures have been introduced for the treatment of angina pectoris. Cervical sympathectomy was introduced by Jonnesco in 1916 and has had a limited application in selected cases. It seems a rather formidable operative procedure in patients with coronary artery disease and disagreeable after effects frequently follow it.

The alcoholic paravertebral injection of the upper thoracic posterior nerve roots gives relief in approximately 50 to 75 per cent. It is apparently free of most of the ill-effects of operation. Since this procedure affords only sympathetic relief, the patient must be followed by continued care to avoid unnecessary strain, as the warning signal of angina may have disappeared.

The treatment of each case of coronary disease is more or less an individual matter, and it is, therefore, difficult to propose definite regulations applicable to all instances.

It is now well established that a recovery from the acute manifestation of coronary occlusion is possible, and life may be prolonged even beyond ten years. In some instances complete recovery, as far as all subjective clinical symptoms are concerned, has been reported by careful observers.

## SUMMARY

The knowledge that has developed in regard to the coronary artery and its relation to heart disease during the past three decades is largely the result of careful studies and investigations by clinicians.

This fact is presented so well in the recent interesting address of Herrick,<sup>82</sup> the eminent clinician who has been foremost in contributing to our knowledge on this subject. He also quotes the prophecy of Scott, who says: "Medical history of the future doubtless will record as one of the important contributions to clinical medicine of the past twenty years the general recognition of coronary thrombosis."

With all this accumulated knowledge the coronary problem in heart disease, in some respects, is still unsolved; the unknown factors are more concerned with its pathologic background than in its clinical expression. When the cause of arteriosclerosis and hypertension is better understood, we shall have advanced still farther in our knowledge of coronary artery disease.

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SEVERE ANEMIA, MYELOCYTOSIS, NORMOBLASTOSIS,  
SPLENOMEGALY AND FEVER (LEUKANEMIA)  
WITH PROMPT RECOVERY FOLLOWING  
TRANSFUSION OF BLOOD

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THE term "Leukanemia" was first used by von Leube in 1900 to designate a blood-picture showing severe anemia of the primary type with a relatively large number of myelocytes in the circulating blood. In the same year, Arneth reported the case of a boy who, following a febrile illness of about three weeks' duration, was found to have a primary type of anemia together with leukemic findings in the blood.

In 1906, Morawitz reported the case of a fifteen-year-old boy who had a leukanemic blood-picture associated with a severe infection of the throat. He had a moderate general glandular enlargement and an enlargement of the spleen, though the splenomegaly was not extreme. After treatment in a hospital for twenty days, the administration of arsenic and general supportive measures, with a persistence of the anemic and the myelocytosis and a steady downhill course in the patient's general condition, a transfusion of defibrinated blood was given. There was a prompt general improvement, and a rapid reversion of the blood-picture to normal. From the data presented in Morawitz's article I have constructed Chart I, which shows graphically the very remarkable changes in this patient's blood.

In 1926, Eimer reviewed the subject of leukanemia, and reported the case of a sixty-one-year-old man who died of the condition. There is nothing of added interest in the case report except that the percentage of normoblasts in the circulating blood reached the high figure of 35 per cent. The autopsy findings were in keeping with those of all of the cases of true leukanemia that had come to autopsy, in that the bone-marrow was entirely lacking in the changes that are found in leukemia. In his discussion of the condition, Eimer points out that it must be differentiated clinically from pernicious anemia, leukemia and acute leukemia. He calls attention to the fact that

myelocytes are found in the peripheral blood in small numbers, about 1 per cent., in severe anemias, while they reach much higher figures in leukanemia. He remarks that pernicious anemia associated with leukemia is not true leukanemia, and suggests that this condition should be spoken of as "the leukanemic blood-picture." The same blood-picture has been seen in injury to the hematopoietic system from tumors of the bone-marrow, intoxications through the bloodstream, *etc.* Simon's case of fracture with secondary coccus infection and a leukanemic blood-picture which disappeared after amputation doubtless belongs in this group, as do Marshall's case of acute miliary tuberculosis and the case reported by Seeman and Krasnopolski of carcinoma of the stomach with metastases to the ribs and the long bones, both of the patients showing the leukanemic type of blood-picture.

In summary, Eimer undertakes to define leukanemia as the blood of pernicious anemia plus that of leukemia, associated with infection, enlargement of the spleen and lymph-glands, and postmortem findings that show necrotic areas in the liver and spleen but absence of the usual changes that occur in leukemia.

Seeman and Krasnopolski are not inclined to concede that leukanemia is a clinical entity, but contend that it should be looked upon as an hematologic symptom complex, resulting from various insults to the blood-forming organs. They describe its mechanism as first, an insufficiency of the blood-forming organs and secondarily a reactive hyperplasia resulting in the pouring out of immature red and white blood-cells.

On January 14, 1929, I saw in consultation an eleven-year-old girl who had been ill for two weeks with fever, headache, nausea, general malaise and weakness. It was thought that she was ill with influenza. Three days before I saw her she had suffered a severe epistaxis, the bleeding having been so free and prolonged as to have greatly alarmed her mother. Her fever had ranged from 102 3/5 to 104.

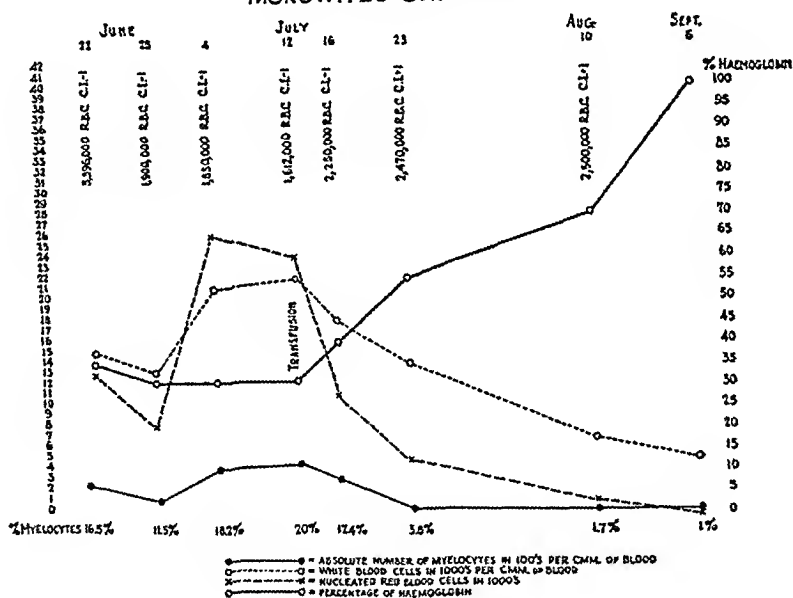
The family history was without significance.

The child's past history was peculiarly negative. She had been of robust health, and had suffered from no acute infectious diseases except measles, mumps and whooping cough. Her diet had been a varied and wholesome one with a full allowance of dairy products,

vegetables and fruits. Her most recent weight had been recorded at eighty-nine pounds.

On *physical examination*, the child was found to be lying in bed, weak and pale, but with no indications of discomfort other than a moderate polypnea. The skin was free of eruptions and abnormal pigments. There were no petechiae. The eyes were not prominent; the pupils were dilated, equal and reacted normally; there was no icterus of the sclerae. The nose showed no obstruction on either

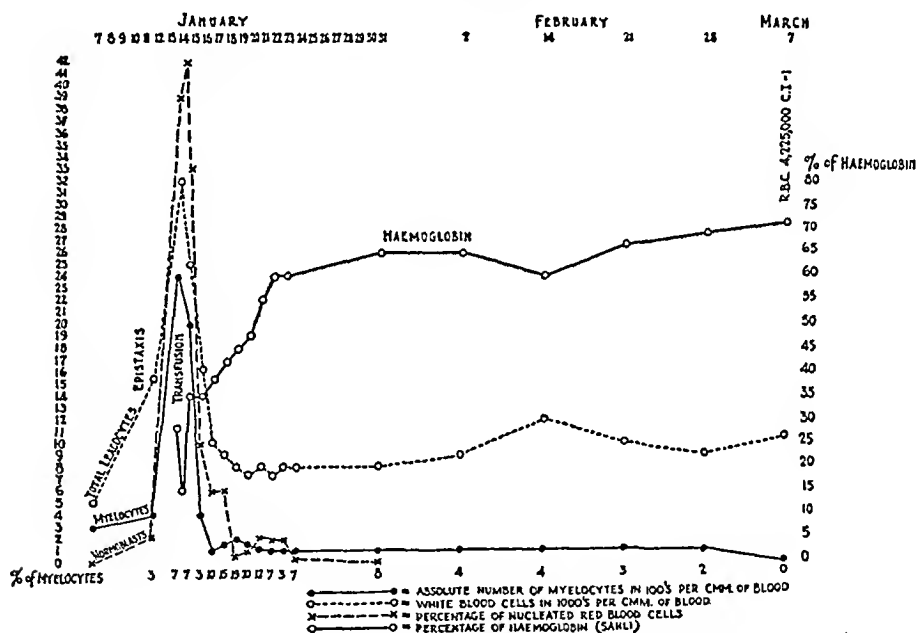
CHART I.  
MOROWITZ'S CASE-1906



side, but there were blood crusts on both sides. The ears were negative. The dental condition was normal. The throat was mildly injected, the tonsils not infected, and there was no postnasal drip. The buccal mucous membrane was normal. The posterior cervical lymph-glands were about as large as French peas; the axillaries and apitrochlears were not enlarged, and the inguinals were just palpable. The heart showed no precordial bulging; a slight thrill was palpable at the apex; on percussion the left border of the heart was just outside of the nipple line; there was no enlargement to the right and there was no dulness behind the manubrium. There was a fairly

loud systolic murmur at the apex which was transmitted for a short distance toward the axilla, but which was better heard at the pulmonic area. Neither of the second sounds was accentuated, and there were no diastolic blows. The lungs were perfectly clear on auscultation and percussion. The abdomen had a full appearance, with definitely more fulness visible in the upper and middle quadrants. On palpation this fullness was found to correspond to a hugely enlarged spleen, reaching anteriorly almost to the mid-line of the abdomen and below to a point almost on the level of the iliac crest.

CHART II.



The liver was not felt; there were no other masses; there was no free fluid, and there was no tenderness. There was no edema of the extremities. The joints were negative. The tendon reflexes were normal. The blood-pressure was 100 (systolic) and forty-five (diastolic). The pulse was 130 to 140 and regular. The temperature was  $101\frac{3}{5}$  at 11 A.M. An ophthalmoscopic examination revealed no abnormalities.

The laboratory studies were as follows:

*Urine:* S. G. 1014; acid; albumin positive; no sugar; a few pus-cells and an occasional granular cast on microscopic examination. Repeated tests for Bence-Jones bodies were negative.

*Stool:* Occult blood test strongly positive; no parasites or ova.

*Blood:* At 11 A.M. of January 14th, the white blood count was 32,000 and the hemoglobin 28 per cent. (Sahli). At 5 P.M. of the same day, the red blood count was 1,400,000; the white blood count 25,800 and the hemoglobin 15 per cent. (Dare). The clotting time was four minutes. The differential count showed: polymorphonuclear neutrophils 57 per cent.; small lymphocytes 30 per cent.; large mononuclears 2 per cent.; transitionals 3 per cent.; neutrophilic myelocytes 7 per cent.; and eosinophilic myelocytes 1 per cent. The red blood-cells showed marked variation in size and shape and many of them showed granular degeneration. The tremendous number of nucleated red blood-cells was astounding. We counted 42 normoblast for every 100 white blood cells in making the differential. The blood platelets were definitely increased in number.

The blood culture was negative.

The Wassermann reaction and Kahn tests were negative.

The Widal reaction was negative.

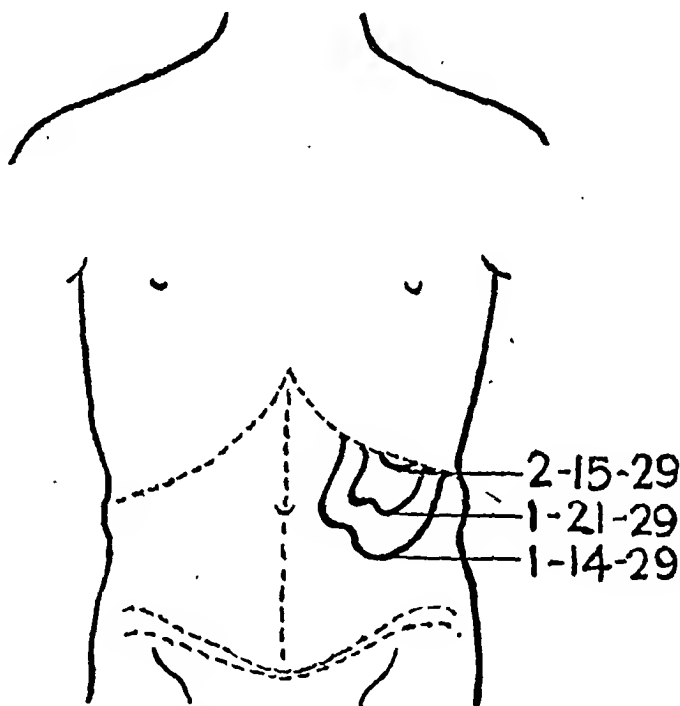
At 7 P.M. on January 14th, the child was given 500 cubic centimetres of citrated blood from her father. There was a slight rise of temperature following the transfusion, but no constitutional reaction. From this time forward the patient made a slow, but steady and uneventful recovery. The changes in the blood-picture and in the size of the spleen are shown in the appended charts. On August 6, 1929, the patient weighed 107 pounds, there was no enlargement of the superficial lymph-glands, the spleen was not palpable, the blood showed 72 per cent. hemoglobin, the red blood count was 4,224,000, the white blood count was 10,200 and there was a normal differential formula. The child is now, March, 1931, apparently perfectly well.

As has been pointed out above, there is a radical difference of opinion concerning the significance of the blood-picture that is so typically exemplified by my case. On the one hand, von Leube, Arneith, Morawitz and Eimer have been inclined to look upon the condition as a disease entity; while, on the other hand, Seeman and Krasnopolski and others have declared their belief that the blood-picture represents a reaction of the blood-forming organs to depletion and to toxic and mechanic influences of an unusual character. The fact remains that the blood-picture illustrated by my case is suffi-

ciently unusual to render it a peculiarly difficult diagnostic problem, and features are presented that are not in keeping with any of the usually recognized types of blood disease.

In severe secondary anemias resulting from acute loss of blood or from acute toxic influences, for example, in the profound anemias of pregnancy or the puerperium, it is not uncommon to encounter positive color indices, anisocytosis and poikilocytosis of marked degree and a mild normoblastosis. As Eimer has pointed out, mye-

FIG. 1.



Sketch showing melting of splenic tumor.

locytes seldom exceed 1 per cent. of the white blood-cells in the circulating blood in these anemias. In my experience, I have never encountered a normoblastosis or a myeloblastosis in any comparable to that shown in this patient in any type of secondary anemia. In pernicious anemia, such a myelocytic response is not to be expected, and while normoblasts are frequently found in showers, I have never seen them in numbers to be compared with those that were found in this case, and it is usual to find a full complement of megaloblasts in association with them. No megaloblasts were found



in this patient's blood. The picture is most closely simulated by true myelogenous leukemia, and the clinical differentiation between this condition and leukanemia is only to be arrived at by the course of the disease or the findings at autopsy. However, certain differences in the blood-pictures do exist. In leukanemia the total white blood count is much lower than that which is usually found in leukemia, and the absence of myeloblasts in leukanemia is in striking contrast with leukemia. Finally, Morawitz's case and mine show that the leukanemic patient may recover, while the leukemic ones do not.

The exact parallel between Morawitz's case and my own, both as regards the clinical course and the blood-picture, tends to support the idea of leukanemia being a characteristic clinical entity. Further, the prompt response of both patients to transfusions of blood, with a rapid return of the blood-pictures to normal, suggests that this is a specific remedy applicable to the disease.

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# SOME CLINICAL ASPECTS OF A DIMINISHED CALCIUM UTILIZATION

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THE question of the importance of proper calcium utilization and the effect of a disturbance therein have become of exceeding interest in the past two decades. From the time of the experiments of McCallum and Voegtlein in 1909 in which was demonstrated the relationship existing between calcium mobilization, parathyroidectomy and convulsive seizures, our knowledge has grown rapidly and many hitherto obscure physical signs and symptoms—objective as well as subjective—have now been classified under this group of disturbances. It is interesting to note how gradually, and at times purely accidentally, the grouping came about. Thus, we had at the Neurological Institute in New York City for a number of years a certain type of case of adolescents that was repeated time and time again with the following set of seemingly unrelated complaints:— (1) fatigue; (2) slowness of growth; (3) conduct disorders. One or all of these symptoms were the reason for appearance at the clinic. Year by year we have been adding to the group, and have been classifying its outstanding features. Upon examination appeared many corresponding features in their physical examinations; their blood-pressure was the same; their irritability and myotonia were uniformly low; their level for age; their reflexes were uniformly low; their contractions were uniformly low; their examination disclosed uniformly low levels of calcium below 7.0 mg. per 100 cc. of whole blood. A correlative fact was that in some cases up to 15% of the body weight was composed of fat deposits probably in the pineal gland.

not to occur before middle-life. The deposits in the pineal perhaps accounted for some of the symptoms shown in the genital domain of various patients. Thus precocious puberty and enlarged genitalia were present out of proportion to the usual incidence of these conditions.

Since the beginning of our studies on these cases—some fifteen years ago, other occasional signs and symptoms manifested themselves—particularly in both the smooth and striped musculature domains. These had to do largely with an increased irritability, or over-sensitiveness and lowered threshold to stimuli—and this led to spasticities. So that spastic colitis was frequently met with; a constant irritating cough was an occasional finding for which no cause could be found until the calcium determination disclosed the probable reason in the spasmodic contractions of the pharyngeal group. Constant muscular tension without the ability to repose was a frequent complaint, and was possibly at the basis of the seemingly undue fatigue.

Recently Aub and Salter found that the spastic colitis due to lead intoxication could be exceedingly diminished or the pain thereof mitigated by parathormone injections. This result they attributed to the relief of the spasticity due to calcium metabolic disturbances induced by lead.

Uterine spasms with pain can to some extent also be credited to the calcium disturbance. The reason underlying this is perhaps the fact that menstrual blood, being rich in calcium—up to 16 or 18 mgs. per 100 cc. causes much calcium loss. At any rate, therapy on this basis helps many cases.

Because of the extreme fatigue or the general body tenseness, these patients lose weight, their musculature shows an attenuated character with very little subcutaneous adipose tissue so that the joints are unduly prominent. Added to this, we frequently encounter the spasmodic cough alluded to; X-ray examination of the thorax gives the evidence of calcium deposits in the bronchial lymph-nodes and a clinical picture is finally evolved which much resembles a generalized tuberculosis.

Several instances of this type have since been recognized at one of our sanatoria for tuberculosis and the tuberculosis diagnosis has been withdrawn.

But from our point of view, the most important groups of symptoms were those developed from the nervous system. Previous investigations had shown that both the central nervous system and the vegetative—with a blood calcium deficiency—gave evidence of increased sensitiveness to stimuli,—the lowered threshold probably being at the synapses. At any rate, children and adolescents particularly thus affected, reacted markedly to all types of stimuli and at the same time more intensely than the average. These patients were inordinately affected by environmental changes, temperature variations, noises and disturbances of all kinds; opposition and criticism irritated them and they reacted rapidly to them. And so, because of some words of abmonition or fault-finding or even a glance or attitude denoting this, such a patient would become violently agitated—out of all proportion to the cause. He would shout, or scream, or strike. or throw things about; and attack his aggressor without any sense of judgment arising to inhibit these rapid responses. And so, some particularly overt act would be committed before saner judgment would enter to deter him. One of our patients, in such a moment of disturbance, threw his sister out of a window because of some slightly disparaging remark she had made; another one shot at a group of his schoolmates with a gun that was handy at just the right—or, rather—wrong moment. Immediately after the act, contrition arises, but too late. Thus many criminal cases, assaultive and homicidal in character, have their origin. Another group is comprised of those who show quickness and alertness in responsive speech; in other words, are witty. These witty responses are almost never the result of thought processes but are due to rapid awakening of associations of many kinds, and the retort is actually made before the talker is aware of what he has said.

These behavior types vary from the mildly irritative through the series of various grades of incorrigibility to assaultiveness and to even hypomanic outbursts with homicidal attempts.

The blood-calcium findings in these cases were with few exceptions quite below the low normal values but not down to the tetany level. They were usually between 5 and 7 Mgs. per 100 cc. of whole blood. The exceptions had a normal blood-calcium value, but because the symptomatology of these cases coincided with those

that were definitely hypocalcemic, they were treated on the same basis excepting that no calcium was included in their treatment. The fact of the presence in the blood of a certain amount of calcium was not tantamount, in our opinion, to its utilization in corresponding degree; and the problem of treatment in such cases therefore was one to produce increased utilization. Without going deeply into the details of treatment it may suffice to say that a few years ago the administration of calcium in various forms was at first all that was done. A few scattered cases apparently reacted favorably to this. Later, when we had decided that the utilization of this calcium was the important factor, we used general glandular products—thymus gland and parathyroid in addition—but with little added success, although the conduct vagaries seemed in a measure occasionally to clear up. A few years ago when the Collip parathormone preparation was added to our armamentarium we had for the first time a dependable instrument. Injections, varying in strength and time of administration suitable to our cases, caused almost an immediate change in the varying symptomatology which we had looked upon as dependent on a low calcium utilization. Especially when combined with large doses of calcium the effect of its administration was quickly apparent. The subjective sensation of a lack of muscular tension with attendant relaxation was stated to have occurred shortly after the first injection. As a consequence of this lessened tension, irritability decreased, fatigue disappeared and sleep became more normal. The conduct disturbances became much modified and in some cases, after a week or two of treatment, practically disappeared. To control these results, treatment with the injection was discontinued for weeks at a time and some other bland injection substituted. The irritability with its attendant disturbances returned within a fortnight of the discontinuance. We have not yet determined how soon after a complete series of treatments, recurrences of symptoms take place. Our custom has been to keep up the injections for a few months with intervals of a week's freedom from time to time; then gradually reducing the treatment weeks to two and finally to one a month, with, however, administration of calcium throughout the period. The summer months with plenty of sunshine have been selected for discontinuance of treatment entirely. Our final results will be

occur but are evanescent. For the past four years, parathormone (Collip) was given hypodermatically at intervals with his calcium, with much more effect both as to speed and intensity of result. It is noteworthy that he reached a height of six feet by the end of 1927 and a weight of 167 pounds—an increase of six inches in height and twenty-five pounds in weight in less than two years.

CASE 2.—Young woman, age twenty-six years; lives in Chicago. Examined September, 1921.

*Complaint.*—Difficulty in concentration, because her mind, as she says, "is tense"; great fatigue; acrocyanosis; intestinal spasticity; intense dysmenorrhea; great speed in mental activity though no depth; anemia; easily angered and aroused.

*Previous illnesses.*—Treated for hyperthyroidism in Paris in 1918 with X-ray; appendectomy, 1919.

Family history: mother, migraine; grandmother, enlarged thyroid; grandfather, diabetes.

*Physical examination.*—Neurologic examination negative. *General examination.*—weight 118 pounds, height 5'5", blood-pressure average 140/80, pulse 75; general myotatic irritability and myoidema in marked degree; musculature tense; great rapidity of speech and constant dryness of mouth; highly intelligent and directs her own case, but in the course of this direction seeks aid in every conceivable place with great rapidity in change of judgment and without the patience to try out any one plan for any great length of time; easily angered and irritated by person, place and occupation; cannot relax.

#### Laboratory Examination

Blood: R.B.C. ....	3,500,000	
Hemoglobin.....	75 per cent.	
W.B.C. ....	6,200	
		{ Polymorphonuclears 66 per cent.
		{ Small lymphocytes 30 per cent.
		{ Basophiles 1 per cent.
		{ Transitionals 1 per cent.
		{ Large mononuclears 2 per cent.
		{ Blood sugar 135 mgs.
Chemistry.....		{ Blood calcium 6.8 mgs.
		{ Urea nitrogen 10.5 mgs.
		{ Chlorides 590

Urine: Within normal variation.

*X-ray examination.*—Skull plates thickened; pineal shadow marked; calcification of bronchial nodes very evident. Basal metabolism *plus six*. (Figs. 1 and 2.)

*Discussion and treatment.*—This case presented a number of problems, anemia being the most prominent and the one that was presumably at the basis of the difficulties. At that time (1921) the low blood calcium awakened only a mild interest. The patient was treated for the anemia in the usual way and shortly the blood reached a normal level and remained there with some short intermissions due to bleeding from the rectum. But even with a normal blood, her symptoms hardly became ameliorated. Various glandular products were administered by many different physicians, and all to no purpose. After a few years (1924) when the importance of the low calcium was understood in con-

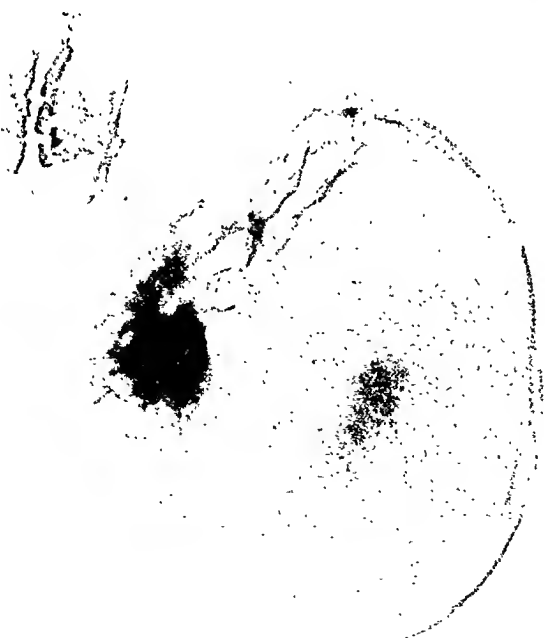
Fig. 1.

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Case 2.—X-ray of chest, showing a number of calcified nodules.  
(Calcium non-utilization.)

Fig. 2.



Case 2.—X-ray of skull, showing rather thick skull tables and a marked  
pineal shadow. (Calcium non-utilization.)





nection with many of her symptoms—notably the various spasticities—the tenseness, irritability, fatigue and mental attitude, her treatment became much modified. Calcium lactate, and calcium in many other forms was administered at first with parathyroid tablets—later with parathormone injections; and for the first time, specific effects were produced. In spite of her vagaries in travelling about consulting various physicians, she frequently wrote in asking that her treatment with parathormone and calcium might be continued for it was the only thing that had ever helped her. Even her dysmenorrhea disappeared, she began to be able to relax and said she even felt “drowsy”—something that was quite a new experience for her. She had had many minor attacks that resembled petit mal which she never confessed but which also disappeared under treatment. During this treatment the blood calcium went up to 9 mgs., (whole blood)—a normal level. She has had many vicissitudes which do not belong to the picture but which have prevented her from becoming absolutely normal, but the improvement is obvious.

*Notes on Course.*—If the X-ray pictures of skull and chest are examined, it will be found that in the case of the skull, the tables show thickening, and the pineal gland is the seat of marked calcium deposit, while the chest shows the calcification of the bronchial-nodes very well. It has seemed to me that in this form of calcium disturbance, in which undue deposits of calcium are found in various parts of the body, that the difficulty is not so much with calcium deficiency as it is with calcium non-utilization. It is these forms that respond rapidly to parathormone injections, while those cases in which the entire skeleton shows a lack of calcification the administration of the vitamins, especially in the form of viosterol, together with parathormone is of distinct advantage. Viosterol alone in this present case, which was tried out, produced an increase of tenseness and had to be abandoned.

CASE 3.—Girl, age eight years. Patient was brought for examination because of tantrums; she strikes and kicks at people about her; threw her six-year-old brother out of the window because of some disparaging remark he made; is very bright at school and witty. Directly after such an outburst she cries, is very contrite and tries to make her peace. Quite fatigable. Many attempts had been made to help her; psychologic approach without any effect; discipline of no avail.

#### *Laboratory Examination*

Blood: R.B.C. .... 4,500,000  
Hemoglobin..... 90 per cent.

W.B.C. .... 7,400

{ Polymorphonuclears	56 per cent.
{ Eosinophiles	1 per cent.
{ Mononuclears	7 per cent.
{ Small lymphocytes	36 per cent.

Platelets: 230,000

Coagulation time: 3 minutes

Chemical blood: (from other sources)

calcium	7.5 (blood-serum)
sugar	110
(others negative)	

Wassermann: negative

Urine: Normal throughout, but specific gravity 1038. pH. 7.2 and 5.4

*Examination.*—Apart from exaggerated reflexes and some muscular inco-ordination she is neurologically negative. *General examination.*—She showed a marked lordosis in the dorso-lumbar spine; myotatic irritability and myoidema marked; height 5' 1 $\frac{1}{8}$ ", weight 72 pounds, blood-pressure 98/76, pulse 86; her thyroid gland is barely palpable; the fundi of both eyes show very full and dilated veins but small arteries; a maxillary torus is present and there is marked general hyperextension of her joints; torso-leg ratio is 36:69.

*X-ray examination.*—Skull: calvarium thin, convolutional digitations clearly visible due to the thin calvarium; sella: normal in size and shape; 8 mm. in antero-post diameter and open, but poorly calcified. No pineal shadow. Chest: shows lordosis of dorso-lumbar spine; no bronchial thickening. (Figs. 3, 4, and 5.)

*Notes on examination.*—This case, in contrast with the first two, while showing similar behavioristic traits of fatigue, tenseness, tantrums and so forth, yet is distinctly different in its X-ray findings. In place of the thick skull tables, pineal shadow and calcified bronchial nodes, it shows the signs of a deficient calcium both in presence and utilization, with thin skull tables, poorly calcified sella, no bronchial-nodes and the signs of a possible early rachitis in the lordosis. It is these cases that do well with the addition of viosterol to the other treatment.

*Treatment.*—The child was at once placed on variations of calcium lactate, parathyroid tablets, viosterol and Quartz light radiation. Because of her intense opposition to hypodermatic medication, parathormone was tentatively withheld especially because of the X-ray findings. On the treatment above outlined improvement began at once, so that in four weeks following its inauguration she had had no tantrums at all for the first time in years. She was much more coöperative and her disposition quite changed. This change in mood and behavior lasted over six months, at the end of which time, because of this improvement, the medication was gradually diminished. It was then begun again in full dosage for a few signs of beginning tenseness became manifest. Almost immediately these signs again disappeared. Occasionally, because of evident kidney irritation due to the calcium administration, the medication had to be discontinued for a week or two at a time. It was finally balanced so that the medicaments were given only during alternate weeks. This occasioned no kidney disturbance whatever and she is still on some modification of this, but in gradually diminishing doses, so that for two or three months at a time nothing is administered at all. The change in the child is remarkable; no more tantrums, no inco-ordination, disposition all that could be desired; myotatic irritability gone and less fatigue. It is interesting to note that in the two years that have elapsed since treatment was begun the child has grown six inches in height.

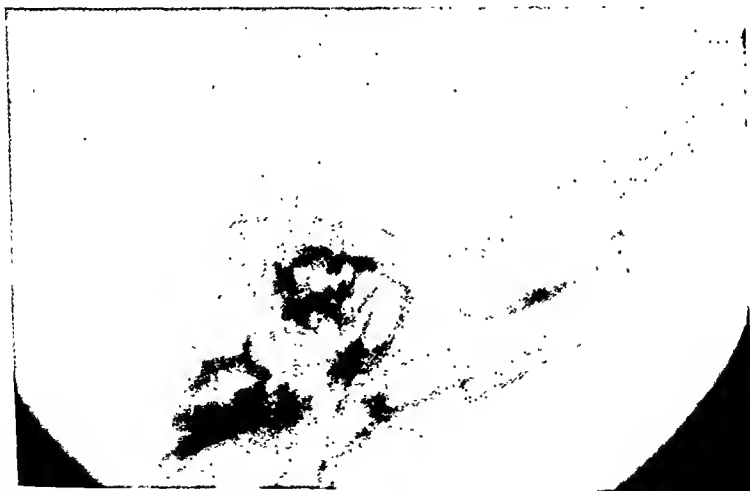
*Summary.*—These three cases illustrate very well the types that are seen corresponding to the syndrome of a disturbed calcium-parathyroid mechanism.

FIG. 3.



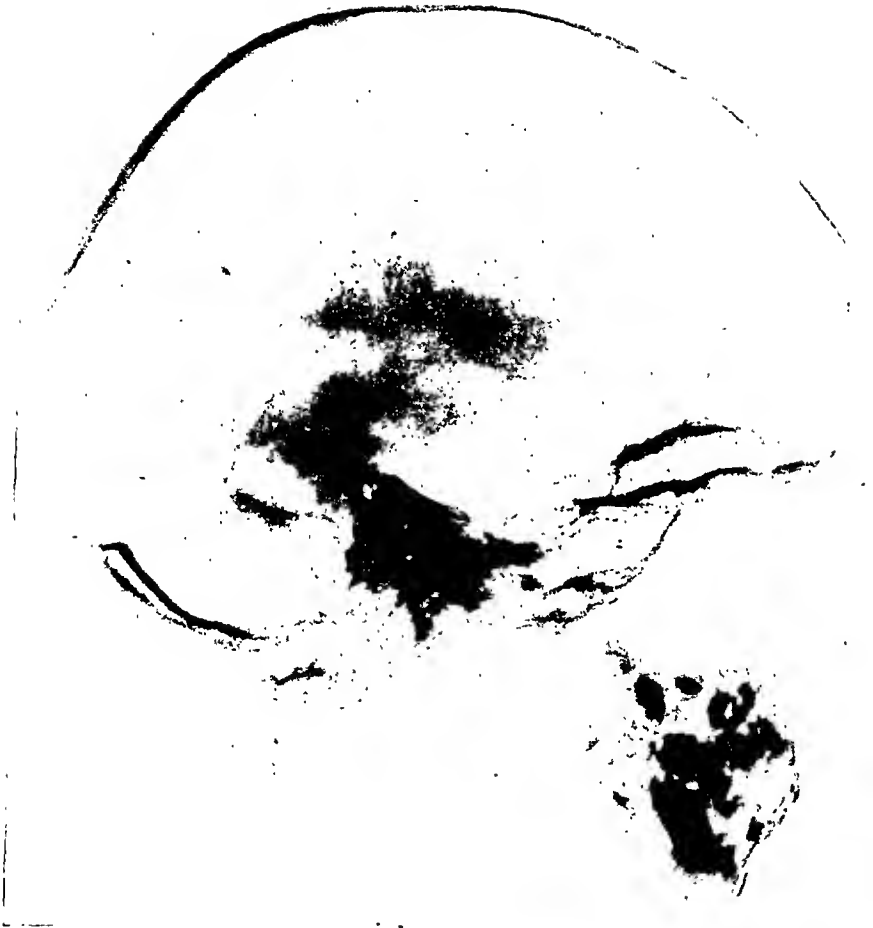
CASE 3.—X-ray of skull, showing very thin skull tables. (Both low calcium as well as non-utilization.)

FIG. 4.



CASE 3.—X-ray of base of skull, showing a general lack of calcification, particularly marked in the clinoid processes of the sella turcica.

FIG. 5.



Convolutional digitations. (Including a softening of the skull tables during early life.)

# SOME PROBLEMS CONFRONTING MENTAL HYGIENE

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MENTAL hygiene has been looked upon as a science, a new religion, a social movement, a series of principles, a body of knowledge, a point of view, a practice or an art and sometimes a fad. It is a human tendency to expect to find in every new thing the hoped-for realization of cherished wishes; hence mental hygiene is given those attributes which suit the special interests and needs of the individual in his untiring search for happiness. This is necessary if man is to learn the potentialities and limitations of any new instrument which he has discovered. It is the primary motivation and the first step in the stock-taking process, hence it cannot be scorned. It uncovers a body of factual material which must be later subjected to careful scrutiny and re-evaluation.

To the physician, mental hygiene is most likely to mean the treatment and prevention of nervous disease, mental disease and mental defect. This was the original goal and still is in need of serious emphasis. It is, however, a negative goal in the sense that it aims to prevent mental disorders. The motive is the wish to avoid the painful consequences of these catastrophes. During recent years, a more positive goal has been superimposed upon this original aim. To seek actively the optimum of social and emotional adjustment for all has become an accepted part of all well-balanced mental hygiene programs. Here the motive is a wish for a positive good which will bring pleasure and happiness. An active search for good health is fundamentally different from the mere avoidance of illness.

Mental hygiene aims at mental health in its broadest sense. This should have special meaning and significance for the physician. As long as its aims were limited to the negative goal the physician contributed a leadership that was necessary and unquestioned since mental disorder belonged clearly in his field. The public and other professional groups were actively interested because mental disorders

with their associated social problems are a concern of all. That the physician held the key to the situation was never questioned. The interest of other groups was viewed as a resource to be called into play for the purpose of advancing a much needed medical program. Positive health programs are not so readily kept in hand. The reason for this difference is not difficult to find.

As long as a program is specially directed towards the sick it is a relatively simple matter for physicians to keep their hands on the helm since the sick seek the physician for aid and counsel. A positive health program is altogether different. One could almost say that a preventive program strives for an avoidance of the need for the physician. This trend is more readily apparent in the mental health field than it is in the field of physical health. Mental disorders carry a stigma that is not carried by physical disorders. There are other factors involved, however. A positive health program is not directed towards a limited group. It involves a service and a teaching for everyone. How can a small number of physicians carry out so extensive a program when they are already burdened with a service to the sick? In the field of public health the problem is simple for although every person has had his own first-hand experience with health problems there is no other professional group that pretends any special knowledge in the matters of physical health. When it comes to mental health and human behavior, not only has every individual had his own first-hand experience but in addition there are several professional groups who hold a very real claim to relevant expert knowledge. As long as mental hygiene had only a treatment goal the leadership of the physician was not challenged but with the assertion of a broader positive goal his whole position is more uncertain and hazardous.

Mental hygiene has aroused a widespread interest which extends not only to many professional groups but to a large representation of the intelligent public. The educator, the clergy, the sociologist, the social worker, the psychologist, the criminologist, the nurse, as well as the physician have turned their attention to this field. It has come to have a professional significance to these groups and they are endeavoring to incorporate its values into their own procedures. In many communities the interest of one or another of these professions

exceeds that of the physicians with the result that in some places the leadership has tended to pass into non-medical hands.

Enthusiastic persons view mental hygiene as the guiding star upon which they place their hopes for the future. To the reactionary members of professional groups it is merely an interesting innovation that "may or may not have something in it," should be viewed cautiously and accepted with hesitancy since it may be dangerous. When one encounters such marked discrepancies of point of view as these, one is warranted in assuming that emotions are in operation instead of reason.

What should be the rôle of the physician in the organization and planning of mental hygiene programs? In the public health field the problem has been answered by training physicians specially for this work. This has been supplemented by nurses, dietitians, social workers and technicians to carry out special phases of the work. The result has been eminently satisfactory. As this health program has progressed we find a number of non-medically trained groups entering the field. The teacher, the physical educator, the athletic coach are good examples. Realizing the values in positive health, they endeavor to incorporate these into their own program. As soon as such trends begin to emerge real dangers such as inaccurate, ill-advised, or even grossly destructive teachings may follow. There is also the possibility of such a program being used as a weapon by groups who are antagonistic to modern medicine. All of these problems should be of great concern to the physician, especially if he believes that his professional training brings with it added responsibilities as an individual citizen at least as far as social planning with respect to health matters is concerned.

For centuries man has looked upon body and mind as being separate entities. During recent years he has come to see them as inseparable. He now sees that they both take origin and can only be fully understood in the light of their common biologic background. Any separation between bodily physiology and psychology is artificial and takes place only in the mind of the individual who conceives them. With his wish to be the superior, rational animal, man has tried to forget his humble biologic origin, desiring to view his mind as significant of something more unique than a biologic process. This same attitude is reflected in his attitude towards his social

problems. He would like to have them occupy a realm of their own which is free from the contamination of a biologic implication. Man does not wish to be held to earth and to the limitations which reality places upon him because of his biologic nature.

Mental hygiene would appear to be an instrument which can serve the purpose of resolving this paradox. In this resolving process the physician's position is crucial because he belongs to the only professional group which is soundly grounded biologically and which, as a profession, is in touch with the individual man at an intimate social level. It is therefore essential that the physician, if he is to meet his obligation, should be prepared to give acceptable leadership in this much broader field.

To try to preëempt it as his own, to try to make it solely his, is impossible since already many other professional groups have valid claims upon it. If he is to succeed in maintaining leadership he must be prepared not only to wrestle with the problems that are more properly his, such as mental disease, but he must, in addition, be willing to lend himself to other professional groups and to acquaint himself with mental hygiene problems arising in other fields. He must become active in his participation. He can learn much from these others while he assists them.

The extent to which routine medical practice is complicated by personal, mental, emotional and social problems is becoming increasingly recognized. One farsighted medical educator plans to attach a psychiatrist to each department of clinical medicine in his medical school in order that the patient as a whole including his total surroundings, may be understood. There are mental, social and emotional factors operative in all cases of physical disorders. When a man becomes a case to the physician, he does not lose his individual personality merely because the physician calls him a case. Because a man is physically ill he cannot deny and dismiss completely his social relationships and obligations, nor his feelings towards them. Frequently these constitute a sufficiently aggravating factor in the total picture as to seriously interfere with treatment and healthful progress. There has been a trend in medicine to look upon the patient as though he were a vegetative manikin. The social and emotional human factors are overlooked in the desire to be objective and scientific. As a result his body has been given what may be



called excellent medical care but the human part of the patient has been neglected and because of this the carrying out of appropriate treatment is often blocked and latent neurotic reactions are called forth. A large majority of routine office practice is made up of the end results of such mistakes. The physician has succeeded in making his patient dependent upon him. Both patient and physician may enjoy this dependency even though neither understands it. It behooves the physician to acquaint himself with the problems arising from the emotional life of his patients, otherwise he cannot understand his patient or how best to work with him. Emotional factors are present whether we recognize them or not. The willingness to permit ourselves to become aware of novel phenomena is the *sine qua non* of the scientific attitude.

There is a close relationship between mental hygiene and psychiatry; in fact, it is difficult to distinguish between psychiatry and mental hygiene. At no point can their separation be complete. Psychiatry means a "soul healing." Healing emphasizes a disease to be cured but psychiatry can be really defined as that branch of medicine which is interested in the study and treatment of human behavior. Some such definition is necessary when we attempt to have it cover the more recent trends. At present psychiatric studies are being made of practically all types of human behavior. Like other branches of medicine, psychiatry has had its brilliant leaders and its periods of rapid progress but on the whole it has tended to lag behind and has not, until recent years, shown much tendency to catch up with the rapid developmental current of general medical progress. All organized professional groups tend to be reactionary. Psychiatry as a branch of medicine is no exception to this.

Psychiatry has tended to remain cloistered within the walls which have held its patients. Even today the staffs of most mental hospitals do not make their influence felt outside of the hospital. In contrast to this, some of the more progressive hospitals have far-reaching preventive programs. Their influence permeates the community and they see mental hygiene as one of their most useful functions, while the reactionary groups resistingly emerge only when mental hygiene organizations press upon them as a coercive force. So while mental hygiene acts in some instances, as a coercive force

upon a reactionary psychiatry, in the hands of progressive psychiatry it becomes a most useful instrument.

Psychiatry has made rapid progress in the last few years. Not only is it attacking its old problem of mental disorder with new vigor but it is also broadening its perspective and relating itself to the social and personal problems that confront the average person. With rapid expansion there have developed conflicting schools of thought. There is a certain incidence of the common human tendency for each group to hold with God-like certainty to the correctness of its own theories, often showing little inclination to consider seriously the merits of differing points of view or to realize that all theories are merely human formulations which we devise for the purpose of reducing the complex facts and processes of life into terms sufficiently simple to prevent overtaxing our meager understanding. Human behavior is too complicated to be safely resolved, at the present stage of our knowledge, into simple formulae. All theories and generalizations, although useful, do a certain violence to the facts of human behavior. Most of the current hypotheses are only points of view from which the ever changing phenomena of human behavior can be viewed to advantage. The only real facts are specific incidents of behavior. The best we can hope for at the present is to find certain common denominators. Each therapist formulates hypotheses that are in line with his own theories and prejudices and the result is that, at times, the treatment reflects the theories of the therapist more clearly than it does the needs of the patient. The neurophysiologically minded physician builds his therapy upon neurophysiologic hypotheses, while the psychologically minded physician builds his upon social and psychologic hypotheses. In a sense this is a shifting of the old body-mind controversy to a new level. Why is it so difficult for man to grasp the concept that neurophysiologic processes and their psychic elaborations are both facts and factors in human life which must be related to each other if any total understanding of human behavior is to be achieved?

There is a tendency in psychiatry and mental hygiene to take the concept of cause and effect too simply and too seriously. Much of our cause-and-effect reasoning is fallacious; for instance, one might say that the street car runs because of the track and the trolley wire. The track and the trolley are joined together at two different points;

first, by a closed system of transmission lines and the generating plant; second, by the complex motor system of the street car itself. The sequences and closed circuits of life and human behavior are much more complex even than this. It is comforting to reduce phenomena to single causes and to base treatment philosophy upon the principle of removing causes. Such a philosophy is an arbitrary one and over-emphasizes the significance of certain factors in what is in reality an unending sequence of unfolding phenomena. Close observation clearly reveals that the number of factors operative at any one point of time are many and that the phenomena are in continual succession and that the terms cause or effect may be validly applied at any point in the sequence and that as the time factor becomes operative, a cause has already become an effect before we may be aware of the phenomena that give indication for treatment. When treatment is undertaken we are generally introducing a new factor into an anticipated sequence of phenomena rather than removing a cause.

Let us take for illustration the surgical treatment of acute appendicitis. In a sense, one removes the cause of the illness when one removes the diseased appendix. Closer observation would, however, reveal that this is not the whole story. In this illness there are the circulation of toxins, the dehydration, the anatomic configuration of the cecal area, the changes in the circulation of lymph and blood in the cecal area; there is the relative virulence of the invading organism and the avenue by which it invaded the host—these are all factors in the illness and are also just as much causes as the offending appendix itself. In fact, the inflamed appendix is an effect of some of these other factors. If we view the surgical interference as the introduction of a new factor into the sequence, we obtain a clearer picture, for, as a matter of fact, surgical interference is the introduction of a new trauma which brings about a change in the relationship existing between the other factors and which, it is hoped, will bring about a change in the undesirable sequences which would otherwise have been anticipated. The skilled surgeon endeavors to modify, favorably, as many other factors as possible, by means of rest, dealing with the balance of fluids and other factors that have to do with the bodily reactions. Here we see a therapeutic program which implies a larger perspective than the mere removal of a simple, single cause.

This discussion would be completely irrelevant if it were not for

the fact that the principles involved are of great importance when applied in the field of mental hygiene. Whether we try to solve the problems arising out of mental disorders by solving the problems of the individual; or whether we try to solve the problems *en masse*, that is, by legislation, social pressure, *etc.*, it is essential to realize that searching for single causes followed by an attempt to radically remove them will generally create more problems than it will solve. For example, ten years ago alcohol appeared to be an outstanding cause of a significant group of psychotic states which required the hospitalization of a large number of individuals. To prevent alcoholic indulgence by means of prohibition seemed to hold the prospect of a very ready answer to a difficult social and mental hygiene problem. But the introduction of this new factor of prohibition did not, as we now realize, remove either the cause or the problem. Alcoholic psychoses are nearly as frequent as before. In many of their present-day aspects they present more serious problems than they did ten years ago. In addition there have been other unanticipated consequences which have followed the introduction of this new factor of prohibition. The behavior of individuals and the reaction patterns of society are very complex. There is great need for a fuller understanding of all the factors involved and the subtle dynamic relationship existing between them. Research should endeavor to establish the facts that are involved so that the sequences of these phenomena may be better understood. It must always be remembered, however, that facts are one thing, while interpretation of their significance is a totally different thing. Assigning meaning to facts always holds a hazard because the validity of the meaning is no greater than the ability of the interpreter to interpret. As soon as one attempts to formulate a corrective program, this source of fallacy immediately enters. All the consequences which may follow the introduction of any new factor cannot be accurately anticipated unless previous experimentation has been carried on with all the facts and factors involved. At the present time we believe we can explain episodes of human behavior in retrospect. A full understanding of all the factors and their relationship to each other would make it possible to forecast accurately future sequence of behavior. We can do this at present only to a very limited extent because of the limitations of our knowledge.

So far our discussion has dealt primarily with the therapeutic or

medical aspects of the subject. Mental hygiene is also concerned with the process of education and with some of the instruments that are used for social and political control. These three aspects of mental hygiene cannot be sharply separated from one another and yet there is need, for the sake of clarity, to deal with them separately.

There has always been a tendency to confuse education, in its broadest sense, with what we might call "mere schooling." Education implies a drawing-out process in which we endeavor to call forth the best that is potential within the individual. In this sense education begins at birth and should not end until death. It includes not only the influence of schools upon the individual but also the influences of the home, of his friends and of such other forms of social and political control as are brought to bear upon him.

The infant brings with him at birth certain potentialities as to height, skill of motor coördination, level of intelligence, internally determined urges to act or respond to appropriate outside stimuli, and perhaps height and breadth of threshold, of emotional response. It is the function of education to draw out these potentialities so that they develop to their optimum. The central nervous system is the integrator of all these potentialities. The cerebral cortex makes possible a wide variation of patterns while the nature of the physiology of the individual neuron determines the elements which may enter into the pattern that is finally expressed. Two conflicting trends are inherent in the function of the neuron. The one, the function of transmitting neural impulses (a tendency to act); the other, the function of inhibition or blocking neural impulses. Throughout the entire human organism these two basic trends become amplified and integrate into most complex systems of impulses towards action or tendencies towards inhibition. The human character of these patterns is relatively determined at birth. The detail of the patterns arises out of the experience of the individual. It is the principal function of education to draw out and assist in the integration of them so that the patterns developed may bring a maximum of satisfaction to the individual with a minimum of conflict with his environment.

From earliest infancy the impulses are expressing themselves. At times this expression is followed by pleasure; at times by pain. Some modes of expression are approved by the environment; some

are disapproved. During early childhood pain, fear and love are the chief forces within the individual that influence the impulses and tend to bring them under control. At least these are the words used by the individual to describe the conscious phase of the process whereby social interaction conditions and reconditions human behavior patterns. In the home, in the school, among friends and throughout youth, these subtle processes are at work fashioning and shaping, developing and destroying individual potentialities.

This whole developmental process is of tremendous concern to mental hygiene. Whether one attempts to prevent delinquency or nervous and mental disease, one finds oneself going farther and farther back into the developmental trends of the individual until one gets back to hereditary factors and to methods of directing the earliest developmental trends of the child. In an attempt to understand and prevent these more serious catastrophes, mental hygiene clinics have been set up for the study and treatment of children manifesting unacceptable behavior. Such clinics have found that it is necessary to have four points of view represented if their staffs are to cope adequately with the problems which are presented to them—those of internal medicine or pediatrics, psychiatry, psychology and social work. One of the greatest practical difficulties has been to secure an adequate supply of properly trained personnel since the demand for such clinics has grown tremendously in the last five years. These clinical units may be attached to a school, a social agency, a medical clinic, a public health department, or a court, or they may function as independent organizations.

These clinical units have contributed a great deal to the understanding of the child and his social and emotional development. Their accumulated experience reveals a multiplicity of facets to the developmental process and shows clearly the subtle and complex influence of the family upon it. Their techniques for study and treatment have undergone continual revision and have advanced very rapidly, especially under the stimulus of the recent dynamic trends in psychiatry.

With this has come an increasing realization of the significance of the parent-child relationship as it functions throughout the life of the individual. Although parents have been viewed as though they were a homogeneous social institution, recent studies emphasize the extent to which each individual parent, each husband-wife relation-

ship, each parent-child relationship is unique. Each child though possessor of all the potentialities common to a man is yet a unique and individual representative of this species. He is in continual dynamic social relationships with his group. These personal interrelationships provide the force inherent in the process of education. Even the content of what we learn is largely determined and colored by the nature of our relationship to the teacher. The teacher and his teachings may be accepted or rejected. The child may conform or he may protest and rebel. He may, out of admiration, imitate the teacher and accept the intellectual and social patterns for which she stands, or he may endeavor to maintain his individuality and independence at all costs.

The realization of these facts places a heavy burden on education for while on the one hand it must draw out and develop that which is individual, unique, and different in the child, on the other hand it must also foster uniformity and conformity. It is the individual who departs from the average that makes those novel contributions upon which progress is based. It is conformity to the wishes of society that forms the basis of social stability. In a sense it is a case of conformity *versus* individuality, the individual *versus* each one of his kind and *versus* society as a whole, the urge towards the social *versus* the urge towards individuality, likeness *versus* difference and fixity *versus* progress. It is the question of social adjustment and of the survival of the fittest, the rights of the individual *versus* social rights.

Both society and the individual tend to accept those who are like themselves and comply with their wishes, while they both tend to reject those who are different or negate their wishes. Each individual has battles to face in two different functional spheres. There is the constant intra-psychic battle between his primitive impulse to act and his tendency to inhibit or control his actions. This is, as it were, the ever recurring "yes" or "no" or the "shall I or shall I not?" At the same time there is also the battle in the social sphere in which the individual is constantly trying to gain pleasure from others. His wishes must be satisfied. Others should "like him" and "be like him." He is continually making subtle demands for attention, approval or love. If the others do not respond they are punished, coerced or rejected. If he cannot succeed in making them like himself and satisfying to his wishes he rejects them. They are alien. They are his enemies. This social battle wages continually.

the basis of provoking stimuli coming from the environment. We tend to take sides and blame either the delinquent or his environment. Seldom is a careful analysis of both classes of factors made. Even when both classes of data are gathered, our need to sit in judgment and fix blame frequently causes us to overweigh the significance of one set of factors. Delinquents and criminals are not such, however, simply because of their behavior but also because of society's reaction to that behavior. The child with temper tantrums or food fads is brought to the clinic because some adult is afraid or annoyed by this behavior. The delinquent who truants or steals is taken to court because he was caught and some adult disapproved of him and his behavior. The wish to possess and the tempting stimulus is only a part of the picture. Many children steal. Most of them are not caught and even among those who are detected relatively few are taken to court. Why is this the case? What is the difference between the two groups of children? What is the difference in the adult attitudes which they encounter? What is the nature of the interaction that takes place between the child and the samplings of society which the particular child encounters? What is one to attempt to change: the child, his environment or both? In what sequences should the changes be made? To professionally "mind the other fellow's business" is an assumption and a responsibility. Too often we fail to gather sufficient facts and instead give gratuitously a great deal of unsound advice, while believing that we understand what we do not.

Human behavior is complex. The expression of human potentialities is unique with each individual and in each situation. The interaction between human individuals and between the individual and society as a whole is as subtle as it is specific and as significant as it is obscure. Man has done a much better job of modifying his material environment than he has of understanding himself, modifying himself and intelligently directing his human relationships. Mental hygiene needs the best brains available to help it solve a limitless number of serious problems. Its research program must be carried beyond the individual diagnostic and therapeutic level. The problems confronting it are not only biologic, psychologic and pathologic but social, educational and political. Medicine will make significant contributions to mental hygiene as the physician trains himself to relate his thinking and his services to these other fields.



## THE KLIPPEL-FEIL SYNDROME

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I HAD to make a trip to Duluth to learn of the existence of this so-called syndrome. At a meeting there Doctor Gowan presented a typical case and said that the diagnosis had been made very promptly by Doctor Hirschboeck of the same city. I at once realized that I had seen a case of this kind without having been able to label it properly. In May, 1930, I was consulted by a single woman, a clerk, aged thirty-two, on account of psychoneurotic symptoms, largely based upon morbid sensitiveness about her physical appearance. This was rather striking as her head was rather large and appeared to be set on the thorax, the neck being virtually absent. The hair line was very low. There was very little mobility of the head. The occiput was tender to pressure. This condition had been present since birth. She showed no symptom of affection of brain, spinal cord, or cervical nerves. Several roentgenograms were taken by Dr. Hollis E. Potter. He found no change in the skull. He states that from a combination of films made below the chin, through the mouth, obliquely and from the side, one gets the impression of a deficiency in the architecture of the vertebral element on the left side as compared with the right. On the right side the body segments can be made out poorly. The entire right side appears to be amalgamated into one bony spike with incomplete segmentation at the joints. The joints between the bodies as well as the lateral ones appeared fused. It is difficult to make out the detail of the structure of the left side of the vertebrae. The deficiency in the vertebrae begins at least at the level of the second cervical vertebrae and extends down to about the sixth. This gives the effect of a partial dislocation. In the lateral views the axis of the cervical spine is in line with the pre-glenoid tubercle which is more forward than usual. While the cervical vertebrae are fused to a solid rod the seven segments can be made out. The normal number of thoracic and lumbar vertebrae is present. (Figs. 1 and 2.)

Since this condition of the neck has existed from birth and as both the clinical history and roentgenologic findings exclude disease and trauma it is certain that we are dealing with a malformation of the cervical spine. Such malformations were described by anatomists over a hundred years ago, but the first clinical description, a very short one, appears to have been made in 1906 by J. Jackson Clarke.<sup>1</sup> This patient was a boy, four years old, with his chin close to the sternum and the head fixed. "Skiagram showed extensive abnormalities in the form of the bones of the upper dorsal and cervical regions, and a cervical rib was present on each side." In 1912, M. Klippel and A. Feil<sup>2</sup> described a man, forty-six years old, whose head rested on the trunk, with little movement. They had the opportunity to make a necropsy. Only four cervical, eight dorsal, and four lumbar vertebrae were present. The cervical vertebrae formed one mass, with posterior spina bifida. All dorsal and cervical vertebrae had ribs. These authors formulated the following clinical syndrome as characteristic of this malformation: (1) limitation of head movements, (2) low margin of head hair, (3) absence of neck, the head resting on the shoulders. This has properly become known as the "Klippel-Feil syndrome." These authors then favored the view that intra-uterine inflammation or trauma may be the cause. In a later monograph Feil<sup>3</sup> expressed the opinion that the original lesion was a high cervical spina bifida and that pressure and trauma later in fetal life did the rest. The only report to my knowledge from America is from the Mayo Clinic, by T. P. Noble and J. M. Frawley<sup>4</sup> who relate two cases, both with two cervical vertebrae missing. They give a good review of the literature up to 1925. Since then there has been an increasing number of reports, mostly from France and Russia, and a few from Germany. I have found seven papers published in 1930. A German author, H. Heidecker<sup>5</sup> says that there is often partial or complete fusion of the atlas with the occiput. The rest of the cervical spine may be one mass, often with ribs. He comments on the few symptoms but mentions that eventually plexus disturbances may develop. This must be rare, however, and I have not found any description of the cervical nerves in dissected cases but one might suspect a reduction in the number or at least abnormal course of the nerves. P. Ingelrans and J. Piquet<sup>6</sup> reported a case in a girl, fourteen years old, with "no neck." Only the lower

FIG. 1.



Skiagram of "Poker neck" in a patient with the Klippel-Feil syndrome.

FIG. 2.



Skiagram of the cervical and upper dorsal vertebrae in a patient with the Klippel-Feil syndrome.

three cervical vertebrae were distinct, the upper forming one mass. There were also malformations of the forearm and thumb, absence of the right external auditory meatus, and asymmetry of the face. Their second patient, a girl, seven years old, had a similar condition of the neck. A Swedish observer, S. Elowson,<sup>7</sup> describes a short-necked child, one year old, with apparent fusion of the third, fourth, fifth and sixth cervical bodies and of the two lower cervical and two upper dorsal spinous processes. A possible prenatal factor presented itself in the history that the mother had to work much in a bent position during pregnancy.

According to Anton Pytel and A. Saevic<sup>8</sup> some fifty cases have been described. Four cases in females are related by them, the youngest being five years old. In the latter case the six upper thoracic vertebrae were fused, and six lumbar vertebrae of normal shape were present. In a girl of seventeen years there were also atrophy of the left hand and forearm and hypoplasia of the os naviculare.

From Paris a new case is reported by Laignel-Lavastine and A. Miget,<sup>9</sup> in a man, sixty years old, with the appearance of "having no neck" as if the head were set on the thorax. Flexion of the neck was limited, other movements good. There were only four cervical vertebrae, with abnormally long spinous processes and large transverse processes. There were no neurologic manifestations.

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# CENTRAL NERVOUS SYSTEM MANIFESTATIONS OF LYMPHOGRANULOMA

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INVOLVEMENT of the central nervous system in lymphogranulomata either of the Hodgkin or lymphosarcoma type occurs so seldom that it seems worth while to add four additional cases to those previously reported by others. The symptoms manifested by patients so afflicted are not specific for the disease, but are those either of invasion with destruction or of pressure such as one would observe in any other similar pathologic lesion of the central nervous system.

CASE I.—No. 6714, L. M. S., white, male, aged thirty years. Onset, June, 1928, with swelling of face, neck, and difficulty in breathing. In September, 1928, the patient was seen by Drs. T. B. Futcher and C. F. Burnam, of Baltimore, at which time he had numerous enlarged glands in the neck, axillae, and mediastinum; the mediastinal mass was pressing on the trachea and bronchi and caused difficulty in breathing and marked distention of the veins of the neck and the superficial veins over the anterior thoracic wall. A lymph-node removed for microscopic study was reported as being lymphosarcoma. After radium therapy there was a rapid disappearance of the enlarged glands and complete relief of the symptoms. In November, 1928, he came under my care because of an acute respiratory infection from which he soon recovered; in December, he began to complain of pain in the right lumbar region and right hip, which was described as a constant dull ache, not made worse by motion. At this time there was no disturbance of sensation in the extremity, neither was there limitation of motion. The pain steadily increased in severity and extent, radiating to both groins, the left leg, and into the calf of the right leg. He was soon almost bedridden, unable to stand or walk without the greatest discomfort. Roentgen-ray examination of the spine, sacrum, and hips did not reveal any pathologic changes in the bones. Lumbar puncture gave a normal spinal fluid; no block in canal. Because of the peculiar distribution and severity of the pain, and the absence of any demonstrable pathologic cause, it was supposed to be due to pressure on the lumbosacral nerves. He returned to Doctor Burnam in February, 1929, and was given radium over the second, third, and fourth lumbar vertebrae, with complete relief of pain for about two months. After this I did not see him although Doctor Burnam has kindly supplied me with the following data: there was a return of the pain in July, relieved by radiation. In September, 1929, he developed severe pain in the right arm. In October, 1929, there was a right sixth nerve paralysis. In January, 1930, there were definite metastases to the skull. Death occurred the following April,

probably the result of a very severe anemia with hemorrhages. No postmortem was obtained.

*Comment.*—This patient had a marked mediastinal involvement causing definite pressure symptoms, later developing a diffuse adenopathy with pressure on the lumbosacral nerves, with subsequent involvement of the cervicodorsal nerves on the right and metastases to the skull. It is probable that the nervous system involvement in this patient occurred as a result of invasion through the intervertebral foramina with pressure on the nerve roots without manifesting any cord symptoms.

CASE II.—No. 7391, L. R. W., white, male, aged thirty years. Onset of symptoms, March 15, 1930, with sudden severe pain in the right shoulder, right arm, and right upper part of the chest, this followed what the patient considered a missed iron shot while playing golf. He came under my care, May 2, 1930, complaining of the above symptoms. At this time only one small gland was found above the right clavicle. The veins of the right arm, right side of the neck and thorax were quite prominent. The dulness over the mediastinum was greatly increased. The heart was apparently normal in size. The spine was straight, freely movable, with no pain. The right arm was freely movable without pain, but for comfort was carried in a sling. There was no sensory or motor disturbance and no increase of the pain on motion. The reflexes were normal. The X-ray demonstrated a very large mediastinal mass which was interpreted as either a lymphogranuloma or a Pott's abscess. The body of the seventh cervical vertebra seemed to be completely destroyed. The cervical gland was removed and after microscopic examination was diagnosed lymphogranuloma (Hodgkin's disease). The pain was interpreted as being due to pressure on the nerve roots as a result of the invasion and partial destruction of the seventh vertebra.

A spinal fixation was done and deep X-ray therapy instituted, after which the pain completely disappeared and there was a regression of the mediastinal glands. It is interesting that this patient had, when first seen, only one superficial enlarged gland. Two months later, glands were discovered in the inguinal region and there rapidly followed axillary and cervical adenopathy. From this date to January, 1931, he had three series of deep X-ray treatments. On January 17, 1931, it was noticed that the left pupil was dilated more than the right and he complained of headache, nausea and vomiting; the headache rapidly became much more severe and was localized over the right occiput. Within thirty minutes the left hand and arm became numb, approximately one hour later hemianopsia, followed shortly by grogginess and marked stupor. The entire left side of the body lost the sensation of touch, without evidence of motor paralysis. The knee jerk was exaggerated on the left, Babinski was positive and there was a sustained ankle clonus. Before the neurologic examination was completed there was a clonic convulsive seizure, beginning in the fingers of the left hand and rapidly extending to the left forearm, face, leg and foot, and within a very few minutes spreading to the entire right side. This seizure was followed

in rapid succession by other seizures of a general type, lasting altogether for several hours and controlled only by the administration of ether. Ophthalmoscopic examination was essentially normal. Spinal puncture revealed a fluid under tremendous pressure well over 360 millimeters of water, the cell count was normal, globulin slightly increased, the Wassermann and mastic negative. The patient died in a state of coma about thirty-two hours after onset of these symptoms.

At necropsy, by Dr. W. A. Smith, the meninges of the brain appeared normal except for a few calcified plaques in the dura. There was a marked excess of fluid in the subarachnoid space, with the convolutions quite prominent. There was no evidence of meningeal hemorrhage or meningeal neoplastic invasion. After hardening the brain was carefully searched for metastatic growths, hemorrhage, or other evidence of damage, but none were found. The mediastinum was filled with a very large mass of glands closely and thickly matted together, almost completely surrounding the trachea and vessels of the neck, and continuous upward with a large group in the cervical region on both sides. The right lung was atelectatic. Metastatic nodules were observed in the spleen and pancreas. The microscopic picture was that of Hodgkin's disease.

*Comment.*—This patient's first symptom was that of pain in the right arm before there was the slightest adenopathy to suggest lymphogranuloma. Following the pain, evidence of pressure on the venous return of blood within the mediastinum and then a small gland was found above the right clavicle. Before there was marked or generalized superficial adenopathy the mediastinum was greatly involved, destroying the body of the seventh cervical vertebra, invasion of the intervertebral foramina causing symptoms referable to the right arm. Towards the end, showing a marked cerebral crisis with unusual neurologic manifestations occurring rapidly, for which no adequate explanation was found at necropsy. The supposition is that the changes observed in the last two days of life were caused either by the toxic effects of deep Roentgen therapy, or that the mediastinal mass so completely interfered by pressure with the venous return of blood from the brain that the related symptoms resulted.

CASE III.—No. 7299, F. R. Y., white, male, aged forty-four years. Hodgkin's disease diagnosed in February, 1929, although for one year previously he had suffered a great deal with pain in his back and right shoulder, for which all of his teeth were extracted by an enthusiastic dentist. Biopsy of a gland removed in 1929 gave the correct diagnosis. He received radium therapy under the supervision of Dr. C. F. Burnam, of Baltimore, with complete relief of his symptoms and the complete disappearance of his enlarged glands. This patient, however, has exhibited very few enlarged glands and none of them have reached the large size usually observed in this condition. Particularly striking was



the absence of marked mediastinal involvement. Since onset he has had several recurrences of the pain in back and shoulders which is temporarily relieved by treatment with radium.

On December 23, 1930<sup>1</sup>, he complained of intense pain in his back and a tight numb feeling in his abdomen; straining at stool caused unbearable pain. Two days later there was urinary retention and very marked muscular weakness of the lower extremities, with inability to stand or walk. Sensation was definitely diminished over the left foot and up to the knee on the right; there was a definite zone of perianal anesthesia. Reflexes of the lower extremity were absent except a bilateral positive Babinski. Lumbar puncture showed a definite spinal block; the fluid withdrawn gave a heavy globulin reaction but was otherwise normal. After a series of deep X-ray treatments the pain subsided, sensation returned to normal, the marked motor weakness improved and he was able to walk with some assistance.

*Comment.*—This patient had pressure symptoms for many months before the nature of his disease was recognized; this probably occurred through invasion of the intervertebral foramina; subsequently invasion with pressure on the spinal cord caused a complete block of the spinal fluid with neurologic evidence of partial paraplegia. There was no demonstrable evidence of bone involvement. Improvement occurred after deep Roentgen-ray therapy.

CASE IV.—R. M. R., white, male, aged twenty-four years. The patient was admitted to the service of Dr. C. E. Dowman, at the Steiner Clinic, November 22, 1930. In April, 1930, the patient complained of attacks of dull pain under the right shoulder; in October the pain became more marked and spread to the left, since which time it is constant and dull, but on straining it is sharp and shooting. With the spreading of the pain he first noticed numbness, beginning in his feet and extending upward to the level of the nipple, at the same time difficulty in walking was noticed, and on November 15th the patient was unable to walk at all. On November 18th there was loss of bladder control and for two weeks there had been loss of rectal control.

On examination there was a complete motor paralysis of both legs and of the abdominal muscles. Sensation to touch was absent over both legs and trunk up to the sixth rib on the left and to the umbilicus on the right. Knee jerks were greatly exaggerated, the tendo Achilles greatly exaggerated on the right, and normal on the left, abdominal and cremasteric were absent, and Babinski's sign was marked on the right and suggestive on the left; Oppenheim's sign was present on the right and left. Ophthalmoscopic examination was normal. The blood was normal. Spinal fluid pressure was 190 millimeters. Jugular compression produced no rise in the fluid level. Removal of 10 cubic centimeters of fluid reduced the pressure to 30 millimeters. Examination of the fluid was normal.

Roentgenologic examination of the thorax revealed a large mediastinal mass, beginning about the hilus of the lung and extending upward; there was also apparently a definite involvement of the fourth thoracic vertebra. This patient has received deep X-ray therapy, with the result that the sensory level began

to drop, with a return of motion in the larger thigh muscles, and lumbar puncture showed relief of the spinal block.

*Comment.*—The onset in this patient was pain under the shoulder and evidence later of complete motor and sensory paralysis of the lower extremities, with bone destruction, involving the fourth thoracic vertebra, and pressure on the spinal cord from the tumor mass. There was definite cord pressure, with relief of symptoms following deep Roentgen-ray treatments.

#### SUMMARY

Attention is called to the fact that neurologic manifestations may be the very first symptoms exhibited by a patient with lymphogranuloma, and that, with many, there are no discoverable superficially enlarged lymph-nodes which would help in making the diagnosis, although in the majority of patients superficial lymph adenopathy later occurs. With evidence of spinal cord symptoms there is usually marked enlargement of either the mediastinal or abdominal lymph-nodes and (1) extension of the process may occur through the intervertebral foramina; (2) by destruction of the vertebral bodies; (3) tumor formation in the epidural tissue, or (4) as a result of definite metastatic deposits in the spinal dura mater.

# HEPATO-CELLULAR CATARRHAL ICTERUS AND ITS DIFFERENTIAL DIAGNOSIS

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## DEFINITION

HEPATO-CELLULAR catarrhal icterus is a common, usually benign, clinical syndrome, characterized by the presence of an increased concentration of bilirubin in the blood-serum, affecting the characteristic staining of the tissues, plus the associated symptoms attendant upon the basic impairment of liver-cell function.

## PATHOGENESIS

This disease state has caused considerable controversy concerning its pathogenesis, before attainment of our present conception. Stokes and Graves ascribed the disturbance to a gastro-duodenitis with ascending infection via the common duct and subsequent occlusion by a mucous plug. This belief persisted because the great Virchow also subscribed to it. Many clinicians, however, were averse to accepting this interpretation. The absence of any real challenge to the obstruction theory was due mainly to the fact that the disease was so benign that no autopsy material was available. Naunyn advanced his idea of cholangy, an affection of the smaller bile-ducts, without inflammation. Chauffard and Widal were among the first to point to disturbed liver function in catarrhal icterus. Eppinger, too, suspected the presence of parenchymal damage. He subsequently provided the conclusive pathological evidence necessary. During the World War, he was afforded the opportunity of autopsying the bodies of three soldiers, killed in battle, who, at that time, had hepato-cellular catarrhal icterus, with

so few associated symptoms, as to allow their active service. Examination failed to reveal any gastro-duodenitis or mucous plug. The liver was enlarged; though otherwise grossly normal. Microscopically, the polygonal cells were distorted and poorly staining; their nuclei deformed and abnormally stained. The normal arrangement of cells was slightly disturbed, with the central vein somewhat eccentric. Some nuclear detritus was seen between the cells. The lymph-vessels appeared dilated and in close proximity to the blood-capillaries. There was no round-cell infiltration or other evidence of any active inflammatory process. These findings were confirmed by Bauer, on examining a section of liver removed at operation, in a case erroneously diagnosed. Klemperer, Killian and Heyd added further confirmation.

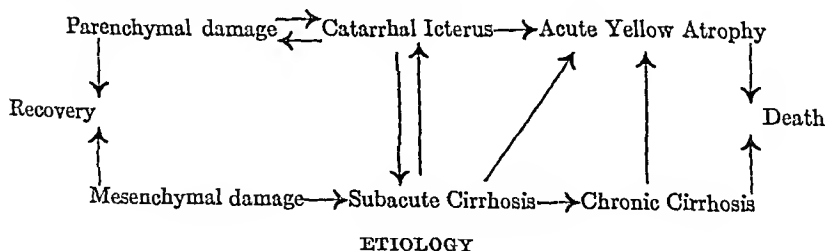
#### NOMENCLATURE

The pathological background being fairly definitely established, the question of proper naming arose. In applying a name to any disease entity, one has recourse to various sources, namely, the etiology, its distinctive pathology, functional disturbance or outstanding clinical manifestation, or combinations of these factors. In "catarrhal icterus," the etiology is still not clear; the pathology, as indicated before, is a degenerative involvement of the polygonal liver-cell, with its associated functional derangement, leading to icterus as its outstanding clinical manifestation. The term "hepathy" with its implication of a diffuse liver affection does not localize the process sufficiently. "Hepato-pathy" is also too universal a term, embracing, however, more the idea of disturbed function. "Hepatitis" is of course unsatisfactory because of its inflammatory connotation.

Rössle has named this condition "hepatosis," utilizing the plan employed by Volhard and Fahr in sorting kidney diseases. From the standpoint of pathological exactness, this term is proper, but the absolute lack of mention of the functional changes ensuing is a real short-coming. The name "catarrhal icterus" combines the adjective "catarrhal" with its description of the type of change going on within the cell, plus the noun "icterus," the outstanding objective symptom. This is a good name, long retained, and adhered to by Eppinger, the only objection being the failure of confining

the catarrhal process to any specific structure—as, liver-cell rather than bile-ducts. Possibly, we may coin the term “hepato-cellular catarrhal icterus” and fill this deficiency, and aid the more accurate development of an immediate clearer mental picture of the entire disease process.

The analysis of liver diseases by Rössle demands our further attention. He differentiates liver disease with parenchymal involvement alone (hepatosis) from disease of the mesenchymal elements. In the former, there can be complete repair or complete destruction, the repair, too, unmodified by connective tissue. In the latter, repair also may follow, but, practically always, the elements of the inflammatory process (new capillaries, fibrin, leukocytes and fibroblasts) leave their mark in the form of scar tissue, of varying extent. As in kidney disease, combined forms and transitions from the one type of involvement to the other are frequently met. It is evident therefore that a patient with liver damage of parenchymal distribution may improve and eventually recover, or else the parenchymal damage progress, and finally destroy the patient. Also, an associated mesenchymal involvement may develop, due to factors still unclear (overactivity of or additional etiologic factors?), leading to various degrees of cirrhosis and its effects, plus more or less associated parenchymal disturbance. These processes may be represented diagrammatically as follows:



The etiology of catarrhal icterus is still unclear. Both sexes are attacked fairly equally, usually during youth or middle age, though the extremes are not immune from assault. The source of the causative toxic elements is not definitely known. The ability of substances, as arsenic and phosphorus, atophan and the specific toxins of the spirocheta pallida to produce parenchymal destruction does not concern us here.

As in any damaging process in the body, the results should be dependent upon the toxic qualities and quantity of the harmful substance or substances, as well as the resistance, or ability of the organism or individual cell to care for them. The patient's tendency to ascribe the onset of the illness to the intake of a specific food has suggested this site for a specific toxin. This belief is opposed, however, by the failure of similar affection of other persons, as members of the family, eating the same food. No infectious basis has been demonstrated. Eppinger found a paratyphoid bacillus in one case, although the etiologic significance of this finding is not very convincing. The absence of true epidemic outbreak also opposes the claims for a specific toxin affection. These facts prompt the suggestion of an altered response of the liver-cell, possibly a disturbance in assimilation, so that substances ordinarily cared for, cannot be handled. This may involve interference with its normal ability to detoxify harmful substances in the food, or the products of bacterial activity in the gastro-intestinal tract. Certainly, the possible existence of a diminished resistance and altered response of the liver-cell would seem borne out by experiences in the past war. An increased number of cases of parenchymal liver damage was noted during that period. There were more cases of hepato-cellular catarrhal icterus and acute yellow atrophy, more icterus during the secondary stage of syphilis, more jaundice following the use of salvarsan—all pointing to increased vulnerability of the liver-cell. This alteration was attributed to the general state of malnutrition, and the associated glycogen deprivation of the liver-cell. The lack of variety in the diet and possible omission of important accessory food factors were also considered operative.

The question of familial predisposition, or tissue susceptibility, is also raised. Catarrhal icterus may at different times attack several members of a family. In one instance, one brother suffered an attack of catarrhal icterus, which cleared after six weeks, only to recur one year later, proceed to acute yellow atrophy and death. Two years later, another brother developed catarrhal icterus. Whether groups of this type reflect a real predisposition or merely chance, cannot be stated definitely.

The rôle played here by the vegetative system (electrolytes, endocrines, autonomic nerves) cannot be evaluated. The tremen-

dous control of the liver by this system would favor its implication. The occasional case of jaundice which appears to follow psychic trauma would also point in that direction. It is possible too that the increased outbreak of cases, during and following the War, was related to the great psychic and emotional traumata experienced, with its background of effect on the vegetative system.

#### PHYSIOLOGY AND FUNCTIONAL PATHOLOGY

In order therefore to appreciate, with greater clarity, the disturbances following upon this impairment of the functions of the hepatic epithelial cell, it is essential to review briefly the physiology and functional pathology of this structure, only insofar as it produces symptomatic disturbances or aids in diagnosis.

The hepatic cell, as McVicar states, represents a workshop of a multiplicity of activities. Bile, the product of its activity, has been the subject of many investigative studies. Brugsch and Horsters emphasize the fact that bile is largely an excretory and not a secretory product of the liver-cell. They found in the elimination of water an antagonistic action between the liver and kidney. In hot weather, when less urine is excreted, the bile is richer in water. If a diuretic is administered and renal outflow increased, the water in the bile is diminished. Uric acid present in the bile is decreased, when its concentration in the urine is increased by atophan. Another claimed proof that bile is largely excretory is the change in specific gravity, dependent upon changes in metabolism. The persistently alkaline reaction they also consider evidence of an excretory function, as also the bile content of certain minerals, such as calcium and iron.

Among the constituents of bile demanding our attention, the pigment, bilirubin, is most important. A tremendous amount of work was done before attainment of the present store of information. Prior to the time of Virchow, the conception prevailed that bilirubin was formed exclusively by the liver-cells. Morgagni had hinted clinically at the possibility of extra-hepatic jaundice as early as the seventeenth century. The first evidence to favor this was presented by Virchow, in 1847. He discovered crystals in blood, extravasated into the tissues, strongly resembling bilirubin, but lacking proof, named the substance hematoidin.

Chemical proof of the identity of bilirubin and hematoidin was later furnished by Jaffee, Fischer, and recently, Bumstead. The epochal findings of Virchow did not attract their deserved attention, and such work as that of Minkowski and Naunyn preserved the longstanding hepatic theory of bilirubin formation. The inability of these experimenters to produce jaundice in hepatectomized geese, in which hemolysis was produced with arseniuretted hydrogen, led them to conclude "without liver, no jaundice." This belief remained unchallenged for many years. Löwitt working on hemolysis in frogs found suggestive deposits of iron and bilirubin in Kupffer cells. The work of Minkowski was subsequently repeated by McNee in Aschoff's laboratory, with identical results, but now with a new interpretation. McNee reasoned that it was the absence of the Kupffer stellate cells, which form so large a portion of the reticulo-endothelial system in geese, that prevented the development of jaundice. The other cellular members of this system are those lining the sinuses of the spleen, the endothelium of the lymph and blood capillaries, the capillaries of the bone-marrow, the suprarenals, omentum, lungs, hypophysis and the macrophages of the blood. McNee was the first to attract attention to the importance of this system in bilirubin formation.

To Whipple and Hooper goes the credit for stimulating the researches which presented the main proofs for this thesis of extra-hepatic bilirubin production. Their work in Eck-fistula animals, however, was not considered absolutely conclusive. The ingenious experiments of Mann and his co-workers on dehepatized dogs gave absolute proof. Universal confirmation followed, with Makino and Rich outstanding. Several workers (Mann; Ernst and Szapanyos; Komari and Iwao) demonstrated increased formation of bilirubin in the spleen and bone-marrow after injecting hemoglobin into the blood to these sites, and in the perfused spleen. The additional conclusions of Mann and his co-workers, that the sources of formation are almost exclusively spleen and bone-marrow, do not seem warranted when applied to the intact animal. Although it seems true for the dehepatized dog, the Kupffer cells here are missing. The presence of pigment in the lungs associated with infarction there; jaundice associated with intraperitoneal hemorrhage, and regional jaundice (Umber and Rosenberg), all point



to the ability of the reticulo-endothelial system everywhere to carry on this function. Also, Makino, and Kodama, in experimental icterus, demonstrated bile pigment in the Kupffer cells before it reached the serum, even before it could be found in the epithelial cells of the liver. The stellate cells contained much more pigment in mechanical icterus than in the hemolytic type. Lepehne, and Eppinger believed their attempts at blocking the reticulo-endothelial system with substances, as collargol, resulted in diminished activity in the process of bile-pigment formation. Rich, in tissue culture studies, found only mesodermal cells capable of transforming hemoglobin into bile-pigment, and this intra-cellularly, possible via an hydrolytic ferment.

The contrary claims of the Minkowski school, now defended by Rosenthal, Melchior and Licht, who failed to produce jaundice in hepatectomized dogs, after the injection of toluylenediamine, were largely vitiated by such experiments as those of Joanovicz and Pick. These indicated that the main effect of such poisons was on the liver-cells. Lubarsch also favored the epithelial cell formation, noting that bilirubin was present in metastatic cells of liver carcinomas. It is quite likely, however, that these cells merely take up bilirubin formed in the reticulo-endothelial system, as normal hepatic cells do.

It is apparent therefore that a fair analysis would indicate the truth of the following statements: First, *that bilirubin is derived from the hemoglobin of the red-blood cell*; secondly, *that this transformation probably occurs in the cells of the reticulo-endothelial system*; and, thirdly, *that the hepatic epithelial cell acts merely as an excretory means for this substance*. Jaundice may result therefore from derangement anywhere along this chain of events, from production to excretion. In hepato-cellular catarrhal icterus, with its damage to the epithelial cell, these cells are less able to care for the bilirubin brought them, less absorption and consequently less excretion occurs.

#### VAN DEN BERGH REACTION

In relation to the problem of bilirubin, it is important to discuss here the nature and implications of the Van den Bergh reaction. Utilizing the response of serum or plasma (Barron) to the diazo-

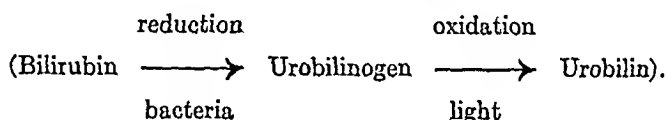
reagent, Hijmanns Van den Bergh described a quantitative test for bilirubin. Qualitative differences are also demonstrable, dependent upon whether alcohol need be added to the serum, before the characteristic color changes are obtained. The direct reaction obtained promptly was found with bile and the blood of cases with liver damage; the indirect, where the addition of alcohol is necessary, in cases of hemolytic icterus. The delayed direct or biphasic reaction was intermediary. Van den Bergh proposed two theories for these differences, first, the existence of differences in the composition of the bilirubin before and after passage through the hepatic cell, and secondly, that indirect bilirubin might be in combination with some substances in the blood, preventing immediate reaction with the diazo-reagent. In evidence for the former theory, the following physical and chemical differences (collected by Barron) are noted: (1) Direct bilirubin is oxidized more readily (Van den Bergh; Andrews) (2) It is more easily adsorbed by the protein precipitate on alcohol precipitation (Van den Bergh) (3) It does not pass into solution with chloroform (Grunenberg) (4) It is dialyzable through a collodion membrane (Hoover and Blankenhorn; Leschke), which fact is probably related to the presence of bile in the urine in cases of mechanical and hepato-cellular icterus, and its absence in hemolytic icterus. Andrews suggested that direct bilirubin was in true solution, the indirect in fine suspension. The claims of Collinson and Fowweather that the direct bilirubin is an alkali salt (ammonium?), the indirect a free acid in colloidal state, and those of Davies and Dodds who believe that the indirect reaction is produced by biliverdin, are not confirmed. The evidence for the second theory of bilirubin-combination is very suggestive. Feigl and Querner suggested a lipoid linkage; Adler and Strauss a protein linkage. Thannhauser and Andersen claim that the addition of bile-salts and cholesterol to an indirect bilirubin serum changes the reaction to the direct. Stüber makes similar claims for uric acid. Barron added to normal human blood-serum increasing amounts of sodium bilirubinate, giving a direct Van den Bergh reaction. Up to twelve milligrams per cent., an indirect reaction was obtained; at sixteen milligrams per cent., a biphasic reaction; above this amount, a direct reaction. He concluded that: "Some constituent of the serum has a tendency to adsorb bilirubin, and this adsorption

prevents the immediate coupling with the diazonium salt." The bilirubin reaching the blood-stream from the cells of the reticulo-endothelial system thus would be adsorbed by some element in the blood, probably serum globulin (Adler and Strauss; Barron), and would give an indirect reaction. The direct reaction would be obtained when substances are present in the blood, as bile-acids, cholesterol and uric acid, in large amounts, which by their stronger adsorbability prevent the adsorption of bilirubin. The latter is then able to react immediately with the diazo-reagent.

Regarding the rôle of the liver in fat metabolism, definite conclusions are also not yet possible. It is commonly known that as glycogen disappears from the liver-cell, fat appears, but whether this is indicative of a metabolic function or a pure catabolic process cannot be stated. The liver is believed to be the site of desaturation of fatty acids, this process a usual preliminary to oxidation. The liver converts the fat molecule into such a state that its potential energy is transformed into dynamic energy (Macleod). The exact place and function of cholesterol in the intermediary metabolism of fat is also not clear. It is widely distributed throughout the body, being especially abundant in the brain and nerve tissue, in suprarenals, epidermis and blood. Blood-cells contain only free cholesterol. Knudson's work indicates that it may act as a conveyor of fatty acids to the tissues. As regards the liver, bile cholesterol must be considered something more than an excretory waste product. The total amount in the feces exceeds that of the food, despite the probable reabsorption in the intestine. Some facts are definite, namely, that it is usually increased in the blood in diabetes, obesity, pregnancy and lactation and occasionally in essential hypertension and cholelithiasis. In the blood, the cholesterol ester is normally two-thirds of the total cholesterol, one-third being free sterol. The esterification is presumed to occur in the liver-cell by the action of a ferment. A cholesterol esterase is also postulated which splits the esters in preparation for excretion in the bile, where only free cholesterol is found. In cases of parenchymatous liver damage,<sup>1, 5, 23</sup> therefore, roughly proportional to the degree of impairment of cellular function, the ratio of esters to free cholesterol in the blood is progressively lowered. Biliary obstruction with its inability to excrete the cholesterol normally present in the bile, raises the blood

figures. Its effect may be modified by the opposing actions of either infection or cachexia (Peters and Van Slyke), which lower blood cholesterol. It is important to note that in carcinoma of the liver, associated with jaundice, although many healthy liver-cells may be present, the blood cholesterol is low.

Urobilin is another substance related to the pigment metabolism of the body. Von Mueller, and McMaster and Elman showed that urobilinogen is the reduction product of the action of bacteria on bilirubin in the intestine. Part of it is reabsorbed and sent to the liver for future use in pigment formation, some into the circulation and excretion through the kidneys. In the urine, the urobilinogen is rapidly oxidized to urobilin.



The threshold of the liver for urobilinogen is limited, and when any liver-cell disturbance exists, even the normal quantity cannot be cared for, more passes into the blood, and thus more is excreted in the urine. The increased urinary excretion obviously can also be effected by an increased destruction of red blood-cells, with its increased production and excretion of bilirubin into the intestine, and increased production of urobilinogen. It is conceivable that in obstructive icterus, where urobilinuria is usually either diminished or entirely absent, bacterial invasion plus the bilirubin in the ducts may result in urobilinogen formation, and its increase in the urine, though absent from the duodenal contents and stool. Certain additional limitations of the diagnostic value are the increase in most acute infectious diseases where there exists no reason to suspect liver damage; the diurnal variation, more being excreted in the afternoon than in the morning; the inability of the kidney of chronic glomerulo nephritis to excrete it, even in the presence of liver disease. It seems evident that an increase of urobilinogen or urobilin in the urine can be utilized as a diagnostic sign of liver or biliary duct disease only in conjunction with other clinical symptoms. The absence of these pigments is, however, much more significant, and indicates failure of bile to reach the intestines.

Bile acids (taurocholic and glycocholic) and their salts are

also products of hepatic-cellular activity. Because of its choline content, cholesterol has been considered the source. Thannhauser was unable to alter the fecal excretion of these substances by administration of large doses of cholesterol. After excretion into the intestines, a great part is reabsorbed and reaches the liver, where it acts as a direct stimulant to the liver-cells. Normally, no bile-salts are found in the urine. In hepato-cellular catarrhal icterus, during the overfunction period (*vide* below) small quantities are excreted by the kidneys. Since bile-acids and their salts are formed in the liver, if their production ceases, it is an indication of severe liver damage. In biliary obstruction, bile-acids are still produced though not normally excreted, and appear in the urine. The itching of the skin and bradycardia of icterus are often attributed to the bile-acid retention, some ascribing cholemia to the excess. Physiologically, bile-salts tend to keep many constituents of bile in solution, and by lowering surface tension aid in the emulsification and absorption of fats from the intestine. Their absence results in disturbed digestion of fat.

Our knowledge of other functions of the liver has been increased by the great work of Mann and his co-workers. In the domain of protein metabolism, they proved that amino-acids are deaminized, and urea exclusively formed there. Clinically, disturbances in this sphere are found only in very acute destruction of the liver.

In the carbohydrate sphere, glycogen is formed from its precursors and stored, dextrose being provided the blood and tissues as needed. Experimental removal of the liver causes an hypoglycemia. Disturbance in the glycogenic function of the liver-cell is utilized clinically in testing the presence of any impairment. Despite the important rôle in carbohydrate metabolism, it must be conceded that most serious liver damage may be present with little or no functional disturbance, with the exception of rare cases of diabetes with co-affection of the liver, and bronze diabetes. Lactic acid is related to the carbohydrate metabolic activities of the liver. Lactic acid, a product of tissue activity, largely muscular, is normally oxidized and reconverted to glycogen by the tissues themselves or transported to the liver for such conversion. In severe liver disease, an increase of lactic acid in the blood therefore may

be found. Schumacher reports a delayed removal of injected lactic acid from the blood of such patients. Here too, however, positive information is obtained only when liver destruction is most marked, and information of little value.

In addition, Whipple showed that fibrinogen is hepatically formed. Quantitative tests are, however, too complex for clinical application. Regarding mineral salts, Haden and Orr demonstrated that sodium chloride may be retained in the liver (as in lobar pneumonia). The metabolism and storage of iron centers about the liver and spleen. A regulatory control over the metabolism of water has also been noted. Tigerstedt found that saline infusions in animals caused enlargement of the liver, persisting until the fluid was eliminated. If the liver was removed, dilution of the blood followed. Molitor and Pick found delay in the elimination of fluid with associated dilution of the blood, in cases of liver damage. Retzlaff suggests that this function is effected via a muscular apparatus of the veins which, on the administration of fluid, increase the pressure in branches coming from the portal vein, enhancing the giving off of water by the blood.

The liver is also said to aid in the destruction of bacteria and their toxins. It removes from the portal vein many injurious agents from the gastro-intestinal tract, detoxifying and preventing their entrance into the systemic circulation. Even in septic liver disease, positive blood culture is extremely rare. The exercise of these functions involves a real danger, for being the first vital organ attacked by toxins of exogenous production, as in food, or endogenously, by bacteria in the intestinal tract, it is constantly open to toxic insults, of the nature herein discussed as causing hepato-cellular catarrhal icterus. And may not the severe types of this disturbance with death follow a complete inability of the cell to care for the various toxins produced in the body?

#### CLINICAL PICTURE

Hepato-cellular catarrhal icterus may affect an individual previously free of any digestive disturbance. Frequently enough to excite attention, persons are affected, who previously complained of "weak stomach" or attacks of "biliousness," mild dyspeptic symp-

toms suggesting the possibility of preceding transient, mild liver disturbance.

The clinical syndrome may be divided into two stages, the pre-icteric and the icteric. The former stage begins fairly abruptly, the patient, often, with a fair degree of certainty, dating the onset, as for example, following a certain meal. The symptoms at this time as a rule are extremely vague—anorexia, frontal headache, and slight epigastric distress. In some, there may be slight elevation of temperature. In the more severe cases, vomiting and diarrhea may mark the inception. Examination usually reveals a markedly coated tongue, with enlargement of the liver already demonstrable. The urine becomes darker, the color often being ascribed to concentration, chemical tests, however, revealing the presence of bile and urobilin. Hyperbilirubinemia is demonstrable by Van den Bergh reaction (delayed direct or indirect) and icteric index determination.

After 3–4 days to a week or more, the second stage begins, with visible jaundice, the face and chest often appearing more icteric than elsewhere. Marked itching of the skin is usually present. The liver enlarges still more; the spleen may become palpable. Hyperbilirubinemia increases, with the Van den Bergh reaction now promptly (or delayed) direct. The stools are deeply colored; the urine contains large quantities of bilirubin and urobilin, and occasionally, bile-salts. This stage, with its content of icterus and large quantities of bile-pigment in the urine and stools, suggests an over-function of the liver-cell, at least, as regards its bilirubin-excreting property. This irritative period may actually be called one of hepatorrhea, analogous to similar processes elsewhere in the body (rhinorrhea, gastro-succorrhea, *etc.*).

The jaundice increases progressively, occasionally with slight drowsiness associated. The pulse remains slow. The liver and spleen may enlarge still more. The period of over-abundance of bilirubin everywhere ceases. The stools may become lighter in color, and rarely may become completely acholic. The activity of the hepatic epithelial cell would seem to be most impaired at this time, with only little bilirubin being absorbed from the blood and excreted into the bile. The bilirubin content of the blood mounts, the Van den Bergh reaction usually promptly direct. The

urine, persistently acid, contains much bile-pigment, though comparatively little urobilin: often, small amounts of albumin and occasional bilirubin-stained casts. Associated with the limited bile content of the intestinal tract, constipation may become prominent. Examination of the cellular elements of the blood reveals no abnormalities; no anemia; no leukocytosis or leukopenia of note. Eppinger reports a slight increase in red cell-count and hemoglobin level (concentration?). The sedimentation rate is normal. Cholesterol figures in the blood are fairly normal in the ordinary case, at worst showing slight diminution, especially in the ester fraction. In more severe cases, the ratio of ester to free cholesterol is more strikingly lowered.

The usual case lasts 4-6 weeks and terminates favorably. During this time, there is constant oscillation in the degree of jaundice, in the color of the stools and urine. The symptoms then rapidly disappear, and the excreta become normally colored. The icterus, clearing more slowly, remains for some time, as the only memento of the illness. The Van den Bergh reaction passes through the cycle of direct to biphasic to indirect responses. On disappearance of the icterus, the patient is entirely well. Occasional recurrences are seen.

#### ATYPICAL CASES

Occasionally, a case runs a long, protracted course, one of ours lasting six months. The onset may be identical with that of the usual case, but without progressive damage, there is a persistence of the icteric state, often without many other associated symptoms. The condition is completely analogous to that of the nephrotic state in renal disease, where the outstanding sign, edema, may persist for a shorter or longer period.

In some cases, the disease sets in abruptly, with severe epigastric pain, often radiating to the right shoulder. This phenomenon is related to marked enlargement of the liver, with tension on Glisson's capsule. After several days, jaundice sets in. Slight temperature elevation is associated—chills rarely. Pain may be so outstanding a symptom as to lead to operative intervention.

An occasional case may begin as usual but fail to show improvement when it is expected. Drowsiness increases progressively.



Severe vomiting arises. Jaundice deepens, with but little bile reaching the intestine. A hemorrhagic diathesis develops. The liver shrinks, evidenced by disappearance of liver dulness. Ascites may develop. Greater damage to the liver-cell is manifested by the marked diminution in the blood cholesterol, with almost absence of the ester fraction; by the appearance of leucine and tyrosine crystals in the urine, resulting from autolysis of liver tissue; and finally, by diminution in the blood urea, and increase in the amino-acids and ammonia content of the blood and urine, as evidences of the disturbances of protein metabolism. Convulsions may set in, coma deepens and death occurs several days later, often suddenly. It is of importance to note that during pregnancy, this progress of hepato-cellular catarrhal icterus to the more severe types of parenchymal liver destruction, is somewhat more common. Adler has pointed out that, in pregnancy, besides these cases of acute yellow atrophy, one meets the usual type of catarrhal icterus and, also, a type of hepatocellular icterus, which may recur with each pregnancy, though of good prognosis.

Also, as Rössle has indicated pathologically, the transition from parenchymal to mesenchymal involvement is met not infrequently. The attack of icterus may not have seemed unusual, but at varying intervals following it, signs of cirrhosis of the liver appear, with its characteristic interference with the portal circulation.

#### LABORATORY AIDS

The clinical pictures presented by hepato-cellular catarrhal icterus thus may be most varied, and often difficult of diagnosis. A discussion of the few additional laboratory aids, of value, would seem in order here.

*Carbohydrate Tolerance Tests.*—The galactose and levulose tolerance tests are used clinically. The galactose test, described by Bauer, is dependent upon the facts that of the common monosaccharides, galactose is most rapidly absorbed from the intestine and removed most slowly from the blood. This explains its propensity to accumulate in the blood, and appear in the urine. Any disturbance in the glycogenetic function of the liver, and therefore the utilization of such saccharides, as galactose, is reflected by its abnormal rise in the blood, and its increased presence in the urine.

Forty gms. of galactose is administered in coffee or water and the urine is collected for the next 12-24 hours. If more than 3 gms. of galactose is obtained, the test is considered positive. Levulose falls between glucose and galactose in its readiness to cause melituria. Though absorbed from the alimentary tract a little less rapidly than glucose, it is utilized only one-tenth as rapidly. Levulose therefore is also used (H. Strauss) in testing the glycogenetic function of the liver. Curves of normal and abnormal galactose and levulose levels in the blood have recently been reported by Fishberg and Dolin. In utilizing these tests, the presence of pancreatic disturbances as diabetes mellitus must be eliminated.

*Ferrocyanide Test.*—Brugsch, working with skin injections of potassium ferrocyanide in cases of jaundice, found a greenish reaction only in cases with hepato-cellular damage. Although recent work has cast doubt on his explanation of the phenomenon, as being dependent upon the presence of bivalent iron, the test appears to have clinical value. A point to remember, in obstructive jaundice, is the appearance of a greenish reaction, only after the jaundice has lasted some time; associated presumably with the development of an hepato-cellular damage. One drop of a 1 per cent. potassium ferrocyanide solution is injected intracutaneously; the appearance of a green reaction after 2-5 minutes is considered positive.

*Water Elimination Tests.*—Interference with the storing and elimination of fluids may be discovered with the following test (Molitor and Pick; Adler). One thousand cubic centimeters of weak tea or water is taken on a fasting stomach. Under normal conditions, the entire fluid is excreted in the urine in 2-3 hours, whereas in liver disease, elimination is slower. Hydremia is associated, evidenced by diminution in red blood-cell count and percentage of hemoglobin. This disturbance is found only in the more severe cases, and cannot be used if complicating cardiac or renal disease is present, especially with edema or ascites.

The use of *dyes*, excreted by the liver, as phenolsulphonphthalein, bromsulphalein, and now tetra-iodo-phenolphthalein, also have their place in indicating the degree of liver damage, and its progression or recession. Tests dependent upon the relation of the liver to protein metabolism, as the protein meal of Cohen and Levin, have not found much clinical value. As a general rule, those tests

based on disturbed metabolic function and least, when needed most, since metabolic activities are disturbed with more difficulty, than mere excretory functions.

The use of the duodenal tube in obtaining duodenal contents and bile may aid in diagnosis. In hepato-cellular catarrhal icterus, bile can be obtained practically always in the early stage in large quantities, later dilute and often requiring chemical detection, and in convalescence, returning to normal. In cholangitis, pus-cells and bacteria may be found. In obstruction by stone, small quantities of bile are obtained, often containing cholesterol and calcium bilirubinate crystals.

#### DIFFERENTIAL DIAGNOSIS

In arriving at a diagnosis of the disease entity, hepato-cellular catarrhal icterus, other diseases which may simulate must be eliminated. A search for the known causes of parenchymal liver damage first must be made. Syphilis can be ruled out by the absence of any active signs or stigmata, and by the negative Wassermann reaction. Most workers believe that the presence of icterus may be associated with a positive Wassermann in the absence of luetic infection, though Kaliski, with a wide experience, denies this.

Those in which pain is prominent must be distinguished from obstruction by calculi. An important differential point is the development of jaundice sooner after the impaction of a stone (hours), than in hepato-cellular catarrhal icterus (days). The liver is larger in the latter, and the spleen more likely palpable. Chills and fever favor calculus; a positive galactose test favors hepato-cellular catarrhal icterus. The excess of bilirubin in the blood and urine is out of proportion to the urobilinogen and urobilin in the urine, when stone is occluding the duct. In this condition, too, the blood cholesterol is usually elevated, while in hepato-cellular catarrhal icterus, it is normal or diminished. The Brugsch test may aid. The duodenal contents may reveal cholesterol crystals, in association with calculus obstruction. However, one must not lose sight of the fact that the two conditions may co-exist. Successful removal of the stones may be performed, but the icterus persists, and raises the question of a complication. The enlarged spleen and positive galactose test then may help. The cases with prolonged

course must be distinguished from cirrhosis and neoplasm, the course usually establishing the diagnosis.

Cholangitis, with its inflammatory background, is fairly easily differentiated. The varying degree of biliary obstruction, with chills and fever is of aid. Duodenal drainage reveals débris, epithelial and pus-cells, and often bacteria, usually of the colon group. The cholangitis lenta (of Schottmuller) can be distinguished on the basis of its large liver and spleen, elevated temperature, marked anemia, negative blood cultures, and finding of pus-cells and the causative streptococcus viridans in the bile obtained on biliary drainage.

Hemolytic icterus can be eliminated on the basis of its increased red-cell fragility, anemia with microcytosis and high percentage of reticulocytes, its indirect Van den Bergh reaction and the absence of bilirubin from the urine, in the presence of marked urobilinuria. Here jaundice is present as an objective symptom, alone, unassociated with the subjective complaints found in hepato-cellular catarrhal icterus, due to the dysfunction of the hepatic cell.

Eppinger has described a form of jaundice which he considers necessary to be differentiated from other forms, especially hepato-cellular catarrhal icterus. He calls this "angina in the region of the papilla Vateri." The condition is characterized by moderate pain in the upper abdomen, particularly in the right hypochondrium, enlargement of the liver and moderate enlargement of the spleen. The disease occasionally ends fatally. At postmortem the liver is found macroscopically and even microscopically normal, but as a cause of jaundice enlarged glands pressing on the papilla Vateri are encountered. Toelg, Neusser and Ryska described similar cases. It is reasonable to assume that the localized glandular enlargement may be due to an infection of intrahepatic structures or the papilla Vateri.

#### TREATMENT

1. *Diet.*—A high carbohydrate, low protein and fat diet is given. This dietetic régime is based upon certain physiologic facts. The feeding of carbohydrates favors the deposition of glycogen in the liver, which is known to protect the cell against assault. Fats are limited, because of their improper digestion and absorption, as-

sociated with the relative absence of bile from the intestinal tract, as well as sparing the liver-cell the task of metabolizing it further. Regarding proteins, it has been shown that they reduce the storing of glycogen in the liver-cells, requiring much liver activity in their complete metabolism (deaminization, urea formation, detoxification, *etc.*).

The carbohydrate content of the diet should reach at least 400 gms. Fruits, as grapes, with their high carbohydrate percentages, are of value. Vegetables are used which do not bloat. No alcoholic beverages are allowed. The protein intake should not exceed 60–70 gms., with vegetable proteins, as green peas, lima beans, *etc.*, given preference. Later, easily digestible animal proteins, as chicken, squab, boiled ham and fish may be used. Fats are given in moderation, and only those easily emulsified, as sweet butter and diluted milk. If vomiting is marked, one may have recourse to other routes for administering carbohydrates—as glucose per Murphy drip, enteroclysis, hypodermoclysis, and infusion, if necessary.

This diet should be given until the patient is entirely well, as evidenced by absence of bilirubin from the urine and normal content in the blood.

2. *Insulin*.—An important therapeutic and somewhat prophylactic measure is the use of insulin. This substance with its promotion of glycogen deposition is of tremendous value and benefit. In early cases, with hyperbilirubinemia and little or no visible jaundice, its use may abort the condition.

If icterus is present, insulin shortens the course, modifies the symptoms and may prevent progress to a more serious state. It has an additional advantage of improving the appetite. Fifteen to twenty units are given twice or thrice daily, one-half hour before meals, with orange juice, to avoid the possibility of hypoglycemic reactions.

3. *Symptomatic*.—The use of calomel, early in the course of the disease, has been advised (Einhorn; Eppinger), 5–10 grains being given in divided doses, and followed by a saline cathartic. The advocates also repeat the doses twice weekly throughout the illness. The calomel favors elimination, and may have a favorable influence upon bile secretions. In cases with diarrhea, calomel should be avoided. The experimental work of Bickel makes claims for the

value of Epsom salts (magnesium sulphate), the sulphate also increasing colonic peristalsis and stimulating the flow of bile. The avoidance of constipation may require enemata.

Sulphur mineral waters are said to be efficacious. The itching of the skin, often very troubling, is favorably influenced by the calomel treatment. Warm baths with bicarbonate of soda, and mild, soothing ointments must at times be used. Enemas of cool water may be of aid. Biliary drainage is of therapeutic value in the protracted cases.

#### SUMMARY

1. The clinical syndrome of catarrhal icterus being due to an affection of the hepatic epithelial cells, the name "hepato-cellular catarrhal icterus" is proposed.

2. It is suggested that an altered response of the liver-cell serves as a basis for the development of this disease. This alteration may be related to hereditary predisposition; to the absence of essential food elements from the diet, or possibly important accessory food factors; or to disturbance of the vegetative system, precipitated by various psychic and emotional stimuli.

3. Analogy is made between the catarrhal process in the hepatic epithelial cell and similar affection elsewhere in the body, with its initial dry stage, second stage of irritative overfunction (hepatorrhoea) and final stage of recession.

4. It is indicated that although the disease usually involves a reversible parenchymal process with ultimate recovery, some cases progress to more severe parenchymal destruction (acute and sub-acute yellow atrophy); others may develop mesenchymal damage and proceed to formation of subacute and chronic cirrhosis.

5. The galactose test and ferrocyanide test are pointed out as aids in diagnosis.

6. The use of insulin and glucose is emphasized, both in the pre-icteric and icteric stages.

# Endocrinology

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## SOME POINTS MAINLY HISTORIC ON THE ENDOCRINE GLANDS GENERALLY AND THE THYROID AND PARATHYROIDS IN PARTICULAR\*

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### INTRODUCTION

THE term endocrine (*ἐνδον* = within and *κρίνειν* = to separate), ductless, or glands of internal secretion, really includes more than is ordinarily understood thereby. According to at least one criterion of an endocrine gland, namely, that the secretion passes directly into the blood and not on to the surface skin or mucous membranes, the bone-marrow manufacturing the red and white blood-corpuscles should be included; but leukemia and erythremia are not regarded as endocrine disorders. Then again the liver has several internal secretions, but it is not considered with the other endocrine glands. This is perhaps because obstructive jaundice is due to disturbance of its external secretion; but here the curious circumstance faces us that to all intents and purposes obstructive jaundice is due to the normal external secretion of bile becoming transformed into a (pathologic) internal secretion into the blood.

The functional activities of the endocrine glands may be disturbed and diverge from the normal in the following directions:

(1) Quantitatively: (a) diminished or complete absence of the normal secretion—*e.g.*, in the case of the thyroid, hypothyroidism, or athyroidism as in myxoedema, cretinism, and cachexia strumipriva; in the case of the parathyroids, hypoparathyroidism, and in the case of the pituitary, hypopituitarism; (b) excessive normal secretion—*e.g.*, hyperthyroidism, hyperparathyroidism, hyperpitui-

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\* This illuminating paper was received on October 29, 1931, and is published without the author having had the opportunity of reading the proofs. By so doing, the article appears immediately, and its publication does not have to be postponed to the March, 1932, volume of the INTERNATIONAL CLINICS.—EDITOR.

tarism, and hyperinsulinism. In contrast to insufficiency, which in many instances can be combated successfully by substitution treatment, for example, by thyroid extract by the mouth, cases of excessive secretion require excision by the surgeon or impairment and partial destruction by the radiologist, and do not yield, as might be hoped, to atropine.

(2) Qualitatively: the occurrence of abnormal secretions often combined with excessive secretion is perhaps less certainly established; but the clinical symptoms associated with altered structure of the endocrine glands differ from those produced by the normal secretion, even in excess, and therefore suggest that the character of their secretions is also changed. This may hold good in exophthalmic goiter and in some hyperplasias, and in tumors of the pituitary anterior lobe, adrenal cortex, and the islands of Langerhans; for example, in exophthalmic goiter the altered histologic structure of the thyroid may be correlated with the presence of symptoms or signs (exophthalmos and gastro-intestinal symptoms) which do not occur when excess of thyroid extract is administered. It should be mentioned, however, that in most exceptional cases exophthalmos and even unilateral exophthalmos (Moorhead) have followed the administration of thyroid extract. The question also arises whether the cachexia of carcinoma of some glands with an external secretion, such as the stomach, may be due to the entry into the circulation—like an internal secretion—of the products of the neoplastic cells. This process would be analogous to the transformation of the normal external secretion of bile into a pathologic internal secretion in obstructive jaundice.

(3) Pluriglandular syndrome: this condition is not so sharply defined as those in which one internal secretion appears to be deficient or absent, as shown by a return to the normal when this secretion is artificially supplied, *e.g.*, thyroxine in myxoedema or insulin in diabetes; it has, therefore, perhaps naturally, invited speculation and some almost romantic hypotheses. Pluriglandular disorder may be regarded as arising in two different circumstances: (a) merely an upset of the endocrine balance as the result of alteration in the amount of one secretion, those of the others remaining normal; thus if the secretion of one endocrine gland becomes deficient the others, though absolutely normal, might become relatively exces-



sive, or *vice versa*. The secretion of the anterior lobe of the pituitary and insulin are antagonistic: in some cases of acromegaly, in which there is overactivity of the anterior lobe of the pituitary, glycosuria occurs. Theoretically an upset of the endocrine balance should occur whenever any secretion is altered: to explain why this does not obviously occur, it is necessary to fall back on some perhaps rather fanciful hypothesis, such as some compensatory action exerted by the other endocrine glands. (b) The other conception of pluriglandular disorder is more obvious, namely, abnormal secretion by several endocrine glands, such as might follow damage by some infection or toxemia, such as syphilis or chronic lead poisoning. Often, however, the conditions ascribed to pluriglandular deficiency can hardly be distinguished from a cachexia involving the whole body, in which there is not any evidence that the endocrine glands are primarily responsible. A prominent result of chronic infections in early life is infantilism, arrest of development and growth; four at least of the endocrine glands—the thyroid, the anterior lobe of the pituitary, the cortex of the adrenals, and the gonads—are specially concerned with the growth of the body, and it is interesting to remember that their influence on normal growth has been made prominent by the abnormalities of growth produced by diseases of these glands. Deficiency of these glands is associated with arrest of development, and their hormones have been likened to growth vitamins. As progressive growth mainly occurs in early life, the effects of disordered function of these glands are more prominent in infancy and adolescence than in adult life. Complete absence of thyroid secretion due to congenital absence or fibroid atrophy causes cretinism; hypopituitarism (both lobes) in childhood is responsible for adiposity of the “pudding-face” type, in adolescence for Fröhlich’s syndrome of dystrophia adiposo-genitalis; atrophy of the anterior lobe of the pituitary causes premature senility, and in extreme instances progeria; a rare result of total aplasia of the anterior pituitary is a progressive and fatal cachexia (Simmonds’ disease or hypophyseal cachexia). Aplasia of the adrenal cortex and probably of the whole of the pituitary is found in anencephalous foetuses. Conversely hyperpituitarism (of the anterior lobe) in early life brings about giantism, and in adult life acromegaly. Hyperplastic adenomas of the adrenal cortex in fetal life are associated

with pseudo-hermaphroditism, in early life induce precocious development of the secondary sex characters and hirsuties, and in adult women "virilism." These examples of the influence of the endocrine glands on growth are of interest in connection with the possibility that pluriglandular deficiencies in fetal or infantile life may be responsible for obscure conditions, such as ateleiosis, progeria, achondroplasia, and its antithesis arachnodactyly.

*The relation of endocrine activity to constitutional states* opens the door to speculation. The thyroid is specially associated with feminine traits, whereas the activity of the pituitary and adrenals may be regarded as associated with masculinity. It has been thought that varying degrees of endocrine function play a part in determining racial characteristics and pituitary predominance to be specially present among the modern Caucasian or European type (Keith), and when greatly in excess to cause pathologic gigantism or acromegaly. Exophthalmic goiter has been considered to occur in people with an emotional constitution, the anatomic basis of which is the status lymphaticus (Marine, 1930). Warthin (1928) described the hyperthyroid or Graves' constitution as characterized by a youthful build, delicate, slender, and soft; with long thin fingers and toes, increased articular mobility, well-developed teeth and nails, and abundant hair. Clinical evidence of the combination of lymphatism and Graves' disease may be forthcoming in enlargement of the lymphoid tissues elsewhere in the body, for example at the base of the tongue. From a histologic examination of a very large number of cases Warthin found that in Graves' disease and toxic goiter there was always hyperplasia of the primitive lymphoid glands in the thyroid, hyperplasia of the lymphatic gland and thymus, and concluded that Graves' disease and toxic goiter represent the abnormal reactions of a primary pathologic constitutional anomaly. Holst regarded the thymico-lymphatic change as secondary to the thyroid disorder, and Scott Williamson and Pearse's researches appear to justify the same conclusions. Writing on heredity in exophthalmic goiter and collecting a number of examples Cockayne concludes that there is an inherited constitutional weakness, a thyroid diathesis, which, in circumstances, such as deficiency of iodine or polluted water, will determine Graves' disease, rather than that there is a direct inheritance of the disease.

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## CRETINISM

The origin of the word cretin, being uncertain, has been variously derived: from chrétien, the Swiss patois crestin or creitin, imbeciles being regarded as Christian and innocent creatures, a human creature, though deformed physically and mentally, in contrast to the brutes; from a Romansh word *cretira* of similar meaning; from the French *craie*, German *Kreia*, or Latin *creta* from their chalky complexion. The great Oxford Dictionary gives 1779 as the date of the first use of the English word cretin by William Coxe.

The association of goiter and cretinism was noticed by Paracelsus (1493-1541) in the sixteenth century in the Salzburg district. The condition was the subject of a Royal Commission which reported to the Government of the quondam Kingdom of Sardinia in 1848; the incidence of cretinism in the district of Aosta was estimated as high as 27.9 per 1,000 of the population, but much lower elsewhere.

There are two forms of cretinism: (1) the endemic occurring in those goitrous areas with the deep valleys in mountainous countries such as Switzerland, Northern Italy, and the Himalayas, and (2) sporadic cretinism or, as it is preferably called in North America, childhood myxoedema, which was not separately recognized until later. The two forms are fundamentally allied, namely, associated with thyroid insufficiency, but between the most characteristic examples of the two forms there are some superficial differences. It is probable that there are transitional forms and that confusion occurs when cases of the sporadic type arise in goiter areas.

(1) Endemic goiter is the result of iodine deficiency in several generations, so that the foetus suffers in intra-uterine life, and as a result there is usually a goiter; De Quervain and others in Switzer-

land have described two forms (*a*) with a large thyroid and nervous symptoms (hypodysthyroidism), which Boothby regarded as resembling exophthalmic goiter, and (*b*) with a small thyroid and without any nervous manifestations. As mentioned above it does not exactly correspond with the distribution of goiter, for it is practically unknown in North America; it would therefore appear that the causation of endemic cretinism differs in some respect from that of the sporadic form, either by the addition of some other factor or by the influence being accentuated and becoming active during fetal life instead of after birth. Whereas removal of the enlarged thyroid in endemic cases aggravates the symptoms and produces myxoedema, in sporadic cretinism the thyroid is nearly always clinically impalpable or very small. It would therefore appear that in endemic cretinism there is either hypothyroidism alone or combined with dysthyroidism rather than complete athyroidism; this fits in with De Quervain's division of the endemic cretins into two categories. Goiter has been described as the parent of endemic cretinism, and just as there are goiter wells, those who drink the water of which becoming goitrous, so there are wells producing both goiter and cretinism in that order. Endemic cretinism is extremely rare in Great Britain, and has apparently died out in some places where it was previously described; thus Hugh Norris reported it in 1847 at Chiselborough in Somerset where in 1871 Hilton Fagge stated that it was disappearing, and referred to its previous occurrence in the island of Arran in Scotland (Reid). Endemic cretinism nearly always occurs in the offspring of goitrous parents, and an enlarged goitrous thyroid is present in the majority of the endemic cretins whereas this is exceptional, but not unknown, in the sporadic cases.

(2) Sporadic cretinism is often, though not invariably, acquired after birth and differs in degree rather than in kind from the congenital endemic form; it has been called childhood myxoedema and ascribed to thyroiditis in early life, and objection has been raised to the use of the term sporadic cretinism. It was introduced by Hilton Fagge (1838-1883) in 1871 in a paper read before the Royal Medical and Chirurgical Society of London during the presidency of T. B. Curling (1811-1888) who in 1850 had pointed out the presence of fatty tumors above the clavicles in a short paper

entitled "Two cases of absence of the thyroid body and symmetrical swellings of fatty tissue at the sides of the neck, connected with defective mental development." Curling did not distinguish between endemic and sporadic cretinism, but he appears to have divined the internal secretion of the thyroid, for he wrote, "I am not acquainted with any case on record in which a deficiency of the thyroid gland has been observed in the human body." Fagge considered that sporadic cretins always showed the presence of the fatty tumors, absence of, or a small, thyroid, and that they could be distinguished from endemic cretins by the absence of symptoms until the period of infancy was over. The last point led him to speculate about the onset of cretinism in adult life—a prophetic recognition of myxoedema. It is interesting to speculate as to the analogy between the supra-clavicular lipomas in cretinism and the multiple lipomas in adiposis dolorosa in which the thyroid has also been found to be affected. Cretinism is rather commoner in females than in males; among 292 cases 172, or 60 per cent., were females (H. Mackenzie).

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#### MYXOEDEMA

*History.*—The first clinical description, based on five cases, of myxoedema was given by W. W. Gull (1816-1890) in a paper entitled "A Cretinoid Condition Supervening in Adult Life in Women," read before the Clinical Society of London on October 24, 1873, and published in the following year. This fulfilled Fagge's prophecy of cretinism supervening in adult life. Gull had long been interested in cretinism and thus had the insight to recognize the occurrence of its features in adult life. On October 23, 1877, W. M. Ord read a paper on "Myxoedema, a Term Proposed to be Applied to an Essential Condition in the Cretinoid Affection Occa-

sionally Observed in Middle-aged Women"; he had watched cases for twelve years, and relied on C. Charles' chemical analysis showing an excess of mucin in the subcutaneous tissues for the suggestion of the name. Halliburton, however, showed that this excess of mucin was not constant in myxoedema, and this is an example of the drawback to utilizing hypotheses for nomenclature. In 1881 Charcot in a clinical account of the disease employed the name "cachexie pachydermie," and in 1898 Osler called it Gull's disease. The early history of myxoedema is well summarized in the very valuable but now somewhat forgotten "Report of the Committee of the Clinical Society of London," appointed December 14, 1883, to investigate the subject of "Myxoedema" under the chairmanship of W. M. Ord; the Report appeared in 1888. On September 13, 1882, J. L. Reverdin read a paper, briefly reported, before the Medical Society of Geneva on the result of total thyroidectomy, describing the symptoms without any reference to their correspondence with those of myxoedema as recognized in England; but in June of the following year with his cousin A. Reverdin he discussed the relation of the symptoms he described to myxoedema, and described the condition as "operative myxoedema." In the meanwhile, namely, in April, 1883, Theodor Kocher of Berne also gave an account of the symptoms under the name of "cachexia strumipriva," but considered that they were due to chronic asphyxia caused by operative injury to the structures in the neck. A controversy, now forgotten, thus arose between J. L. Reverdin and Kocher. Felix Semon (1849-1921) after reading these reports, which had escaped notice in Great Britain, argued at a meeting of the Clinical Society on November 23, 1883, that cachexia strumipriva, myxoedema, and cretinism were all due to the same cause, namely, loss of function of the thyroid gland; this view at first, like so many original departures, ridiculed, was fully endorsed by the Report of the Clinical Society's Committee, on which Semon served, and was subsequently accepted by Kocher. Semon's contribution is not reported in the *Transactions of the Clinical Society of London*, and is indeed rather buried in the report of the meeting in the *British Medical Journal*.

Horsley then in 1884 repeated M. Schiff's experimental thyroidectomy in dogs (1856-1858, republished in 1884) which proved fatal from concomitant removal of the parathyroids, the existence of

which was unknown until 1880. From experiments on monkeys, carnivora, and other animals, Horsley's results were then regarded as evidence that total thyroidectomy produces operative myxoedema; but some of the symptoms, such as "fibrillar twitchings in the muscles going on to violent clonic convulsions affecting all the extremities and the trunk," must be regarded as due to parathyroid insufficiency. Thus the interpretation of the early results of thyroidectomy were complicated by concomitant removal of the parathyroids. In 1888 Horsley showed experimentally that partial thyroidectomy was followed by compensatory hyperplasia of the thyroid; W. S. Halsted simultaneously and independently proved this, but apparently did not publish his results until 1896.

The history of the present successful treatment of hypothyroidism, myxoedema, and cretinism, is brief. Grafting after experimental thyroidectomy was tried by M. Schiff, A. von Eiselsberg, and Horsley who in 1890 recommended it in man. Bircher in 1889 had grafted a piece of human thyroid into the abdominal wall of a patient with temporary benefit. Ewald's injection of an emulsion of thyroid into the circulation, as might now be expected, produced toxic symptoms. In 1890 intravenous injection of a thyroid extract into thyroidectomized dogs was found to give good results (Vassale). In 1891 G. R. Murray, a pupil of Horsley at University College Hospital, then at Newcastle-on-Tyne and later Professor of Medicine at Manchester, obtained benefit from the hypodermic injection of the juice obtained from a sheep's thyroid in a woman. This patient, a woman, aged forty-six, lived till the age of seventy-four, continuously taking thyroid in one form or another. In the issue of the *British Medical Journal* of October 29, 1892, Hector Mackenzie and E. L. Fox independently recorded cases in which the oral administration of thyroid extract was quite effective, and in the same year Howitz of Copenhagen also obtained the same result.

A very large number of investigations were undertaken to isolate the active principle of the thyroid hormone; in 1895 Baumann proved that the thyroid contained iodine, and isolated from it iodothyrene with about 10 per cent. of iodine. This was followed by numerous investigations into the chemistry of the gland. In 1917 Kendall isolated and analyzed a pure chemical substance,

thyroxine, containing 65 per cent. of iodine, and in 1925 Harington synthesized thyroxine.

In 1923 Albert Kocher revived the treatment by thyroid grafting, and in connection with the success of the operation insisted on the importance of keeping the patient under the influence of thyroid extract both before and after the operation of transplantation, otherwise the graft is "simply eaten up" by the subthyroid patient. He reported 214 cases in which thyroid grafts, obtained (1) in a normal state from animals, (2) from the thyroid of Graves' disease, or (3) from the thyroid tissue around a thyroid adenoma, were made. Ten of the cases were patients with congenital absence of the thyroid, and of these three only were really benefited. Of the remaining 204 cases of more or less severe thyroid deficiency, 26 per cent. were entirely cured and did not require to take thyroid at all; 21 per cent. were much benefited but had to take thyroid now and then in smaller quantities, thirty-nine were improved but had to take thyroid constantly though in much smaller amounts than before the operation, and in fourteen cases the grafting was a complete failure. Thus it appears that in a number of cases the graft remains active, at least for a number of years, and Kocher considered that in most cases the patient's own thyroid became active and a cure resulted. If not, a re-grafting was performed; this was done in twenty cases with cure; in eight cases the operation was done three times, and in one instance on four occasions.

*Etiology.*—Myxoedema or adult cretinism has, like other affections of the thyroid gland, always been regarded as occurring far more commonly in females than in males; in fact until 1880, when G. H. Savage reported a male in Bethlem Royal Hospital, St. George's Fields, London, with this disease, it was thought to be confined to women. In exceptional cases in which all the thyroid tissue is in an abnormal position, such as the base of the tongue, its unwitting removal as a troublesome tumor, has been followed by cachexia strumipriva or operative myxoedema.

An interesting sequence is the occurrence of myxoedema in an individual formerly the subject of exophthalmic goiter—diseases generally speaking the opposite of each other. This provides an example of overactivity and hyperplasia succeeded by exhaustion and premature atrophy, or of antagonistic phases of disease over-



lapping each other. In some instances symptoms of exophthalmic goiter and some of those of myxoedema, especially edema, are seen at the same time, as if the transition had begun; and in these cases thyroid extract does good, whereas in ordinary cases of Graves' disease the administration of thyroid aggravates the symptoms of hyperthyroidism. For another explanation of the combination of Graves' disease and myxoedema see p. 235. Gulliver in 1886 reported myxoedema due to thyroid carcinoma and also referred to a cretin, a boy aged eighteen years, with carcinoma of the thyroid. Neither of these observations appears to have been confirmed.

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## BENIGN HYPOTHYROIDISM

Hypothyroidism of a degree not amounting to myxoedema, or an incomplete or fruste form of it, or benign hypothyroidism as Hertoghe called it in 1899, is very common in women, especially at the menopause. Theodor Kocher also described it in 1909 as slight thyroid insufficiency, and his son Albert Kocher in 1923 de-

scribed it to congenital thyroid inadequacy, though symptoms may not appear till later life, after many pregnancies, with the onset of goiter or of toxic or infective thyroiditis after typhoid, influenza, and other general infections, or at the menopause. The symptoms are described by Hertoghe as protean, and include conditions so far apart as obesity, flat foot, chilblains, enuresis, subinvolution of the uterus, rheumatic pains, rheumatoid and osteo-arthritis (Llewellyn), pigmentation of the skin during pregnancy and loss of hair after it, gray hair, constipation, psoriasis, urticaria, a subnormal temperature most pronounced in the evening, and general fatigue (L. Williams). The dependence of the symptoms on thyroid insufficiency is sometimes best clinched by the therapeutic test, namely, improvement after the administration of thyroid extract.

*Treatment.*—In cretinism arrest of growth both of body and mind (infantilism) is extremely well marked; by thyroid medication, or substitution treatment, the effects of athyroidism, or of thyroidectomy, can be obviated, and for the time being the individual is made normal, just as a dose of insulin temporarily transforms a patient with diabetes mellitus into a healthy person, or a dose of the extract of the posterior lobe of the pituitary relieves for some hours the polyuria of a sufferer from diabetes insipidus. But in these diseases, as in cretinism and myxoedema, the administration of the glandular extract is not a cure; this would be provided by the successful grafting and growth in the patient's body of the gland which is deficient in its secretion. Mongols, in the past, often regarded and treated as cretins, are not benefited by thyroid.

In the treatment of myxoedema, cretinism, and hypothyroidism, the dose should be determined for each patient by beginning with a small quantity, half a grain of dry thyroid at night, and working up to that which keeps the symptoms in abeyance and does not cause any toxic manifestations. In cretins under one year the initial dose should be  $\frac{1}{8}$  to  $\frac{1}{4}$  grain of the dry thyroid powder. The administration of thyroid extract diminishes the cholesterol content of the blood which is raised in myxoedema and in other conditions, including mental disorder, especially in apathetic states (Duncan). Chronic nephrosis has been treated with 15 to 30 grains of thyroid daily; these patients are extraordinarily tolerant of large doses of

thyroid extract and thyroxin, much more so than the subjects of myxoedema.

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#### SIMPLE OR NON-TOXIC GOITER

The *history* of goiter (guttur=the throat) was reviewed by A. Hirsch exhaustively, and more recently by Manchester Brown of Milwaukee; as might be anticipated, such an obvious change did not escape observation by Hippocrates who, however, did not differentiate it from tuberculous adenitis; hence perhaps the somewhat generic term "struma" long survived in connection with the thyroid—e.g., cachexia strumipriva. Celsus (B.C. 25–50 A.D.) appears to have been more alive to this point, and this was more definitely realized by Aetius (ca. 500) and Paul of Aegina (625–690). As already mentioned Paracelsus (1493–1541) recognized the association of endemic goiter with cretinism, and Manchester Brown quotes Baccius (1571) to the effect that in Salzburg "the people are strumous, but the women more than the men, because of the evil of the water (as they think) that they drink." Thomas Wharton (1614–1673) in his *Adenographia* (1656) gave both the first good description of, and the present name to, the thyroid gland which Eustachius (1490–1570) spoke of as the "Glandula laryngea"; but Wharton, like Morgagni, Malpighi, and Bartholin, considered that the thyroid provided a lubricating secretion for the arytenoid cartilages and the mucous membrane of the trachea.

*Endemic goiter* has long been ascribed to the water supply, in fact, from the time of Pliny, inorganic substances and glacier débris being suspected. Two explanations of the origin of goiter are current: (i) that it is due to deficiency of iodine, in other words it is a "deficiency disease"; without a sufficient supply of iodine the gland cannot manufacture thyroxin, and as a compensatory attempt hypertrophies. Hirsch, writing in 1883, long before the present revival of the view that deficiency of iodine was responsible for goiter, said, "A short-lived opinion was advocated by Chatin in

1850 (before him by Prevost and Maffoni in 1846) and after him by Marchand in 1850 and Fourcoul in 1851, to the effect that the cause of goiter and cretinism lay in the absence of iodine in the drinking water and air." The deficiency of iodine may be in the water, for example that percolating through limestone, and in the soil and foods; in favor of this correlation are (a) the results of analysis of the water, soil, and food in goitrous districts such as the area of the Great Lakes in North America, Switzerland, other mountainous districts, and New Zealand, and (b) the demonstration by Marine and others that the administration of small quantities of sodium iodide will prevent the occurrence of goiter in schools in goitrous areas. It should be mentioned that Orr's investigations in Great Britain do not show that deficiency of iodine in the food can be correlated with endemic goiter. A method of insuring an intake of iodine in small quantities is that employed by A. Kocher, namely, to place in the sleeping rooms perforated pepper pots containing the volatile iodide of calcium. Foods relatively rich in iodine, such as sea-fish, especially shell-fish, watercress, eggs, milk, and iodized table salt with one part of potassium iodide in a quarter of a million, have been recommended.

(ii) The other view, that bacterial infection of the water causes the thyroid change, has been supported by McCarrison, who believes that simple goiter may also be due to various other causes, *viz.*, deficiency or excess of food, gastro-intestinal infection, insanitary conditions of life, and deficiency of iodine.

The presence of yeasts in the intestine has been suggested as a causal factor (Buchanan). But the important point is that, as Marine has repeatedly shown, iodine in proper quantities will protect against all agents which produce goiter. Webster and Chesney produced a simple goiter in rabbits by a diet consisting almost exclusively of cabbage; this has been confirmed by Marine, Baumann, and Cipra, who suggest that cabbage depletes the store of thyroxin in the thyroid, thus producing a relative deficiency of iodine in the animal and so thyroid hyperplasia. Webster and Chesney protected their rabbits for a year from goiter by giving 7.5 milligrams of iodine a week.

Simple or non-toxic goiter, especially in the young, does not disturb the heart's action and usually does little more than cause

some worry on esthetic grounds; but it may mechanically compress the trachea. Adenomas projecting from the lower margins of the lobes or from the isthmus of the thyroid may pass down towards the chest, become impacted in the upper opening of the thorax, and so compress the trachea and cause urgent dyspnea ("plunging goiter"). Adenomas may arise in accessory thyroid tissue in various positions, such as the base of the tongue or the submaxillary region; but the most important are intrathoracic goiters. Their incidence has been variously estimated between 6 to 32 per cent. of all goiters (Curtis); Lahey reported that among 8,500 goiters 250, or 3 per cent., were intrathoracic. They may be partially or entirely intrathoracic, and give rise to venous stasis in the neck in 15 per cent. Early detection, which a radiologic examination may facilitate, is most important so that they may be removed before they become large or undergo malignant change.

In young children goiter, being usually parenchymatous and containing little colloid, readily subsides when treated with iodine. In goitrous subjects over seventeen years of age iodine fails because the goiter contains much colloid (E. Mellanby). The symptoms of so-called thyrotoxicosis due to excessive dosage of iodine in cases of previously non-toxic goiter are tachycardia, tremor, loss of weight, and raised basal metabolic rate.

*Iodine*, discovered in 1812 by B. Courtois, a soap-boiler in Paris, then further investigated by Clement and Desormes, and by Davy, was employed as a remedy for goiter by C. W. Coindet in 1820. In the following year it was, apparently independently, used by Alexander Manson (1774-1840) of Nottingham, England, in various diseases, the most noticeable success being obtained in goiter. About the middle of the last century goiter was widely treated by iodine, but evidence of bad results, probably due to overdosage, gradually accumulated and it became less popular as a remedy. About 1922 H. S. Plummer re-introduced the iodine treatment of thyroid disease, and considered that it diminished hypersecretion but did not affect the abnormal secretion which he believed also occurred in Graves' disease. Rienhoff and Lewis showed that iodine altered the histologic appearance of the hyperplastic thyroid, bringing about involution and removing the symptoms of hypothyroidism. In 1170 Roger of Palermo, a surgeon of the Salerno school, gave the ashes

of sponges and seaweed (iodine) in goiter or scrofula (Fielding H. Garrison).

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## TOXIC GOITER

Although the goitrous thyroid shows hyperplasia, constitutional symptoms, such as might be expected from an excessive or altered secretion, are often quite absent either permanently or for a long time; but symptoms of hyperthyroidism, resembling in most, but not all, particulars, those of exophthalmic goiter, may supervene, perhaps years after the goiter first appeared and is regarded by H. S. Plummer, who stated that this change will take place in three out of every five persons with adenomatous goiter who live to the age of sixty-five years, as due to hyperthyroidism or excessive normal secretion; this has been called secondary exophthalmic goiter, and is now commonly known as toxic adenoma or toxic goiter. It is generally thought that it may be caused by the administration of iodine to cases of adenomatous goiter, as was noticed by Rilliet in 1859, and it has even been suggested that the prevalence of toxic goiter is partly due to the administration of iodides in therapeutic doses for common ailments (Carmalt-Jones). This would be an argument against the iodination of all municipal water supplies recommended by the Swiss Goiter Commission and to the proposal to make iodine an ingredient of all cooking salt. That iodine is responsible for the transformation of simple goiter has been disputed; N. B. Foster considers that this risk has been much exag-

gerated. According to Plummer diffuse colloid goiter rapidly diminishes under the administration of thyroid extract, and toxic goiter, unlike exophthalmic goiter, is not benefited by iodine or Lugol's solution.\* Youmans and Kampmeier, however, find that toxic adenoma responds to iodine in essentially the same way as exophthalmic goiter, any difference being quantitative and not qualitative, and conclude that no pathologic distinction between them is justified on the basis of their response to iodine.

There is considerable difference of opinion on the problem whether toxic goiter and exophthalmic goiter are one and the same with only the variations that may occur in a single disease, or whether they are distinct from each other, as Plummer, Eberts, and others believe, toxic goiter being pure hyperthyroidism and exophthalmic goiter hyperthyroidism plus dysthyroidism. The differences of toxic adenoma from exophthalmic goiter are that the goiter may exist for years before the onset of symptoms, that it occurs in older patients, that exophthalmos is absent, that its course is often mild, and that surgical treatment is more successful. In its early stages when nervous symptoms and rapid cardiac action are the prominent manifestations, Graves' disease is indistinguishable from hyperthyroidism. This indeed supports Dunhill's and Fraser's view that toxic adenoma and Graves' disease constitute a single disease with transitions from these two extremes; but his suggestion that this disease should be called "toxic goiter" would lead to confusion as it is generally used as a synonym for toxic adenoma. R. S. Morris points out that transient auricular fibrillation may occur as a result of toxic adenoma although the basal metabolic rate is normal, and that in such cases subtotal thyroidectomy may be followed by the same benefit as in cases with similar symptoms and an increased metabolic rate.

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\* J. G. A. Lugol (1786-1851) was a medical man in Paris.

## EXOPHTHALMIC GOITER OR GRAVES' DISEASE

The history of this now familiar disease, which may well have become more frequent as well as more generally recognized, was given by J. W. Legg in 1882, by G. Dock in 1908, and Means and Richardson in 1929. Caleb Hillier Parry (1755-1822), "the distinguished old Bath Physician," observed "enlargement of the thyroid gland in connection with enlargement or palpitation of the heart" in August, 1786, and so preceded Guiseppi Flajani's publication of two cases in 1802 and by many years those of R. J. Graves of Dublin (1835) and Karl A. von Basedow of Merseburg, whose account of the three most important symptoms gave rise to the phrase "the Merseburg triad" (1840). Parry's observations on exophthalmic goiter were only fully published posthumously in 1825, and it was not until 1813, twenty-seven years after he observed the first case, that he correlated the cardiac condition with the bronchocele, but in his "Elements of Pathology and Therapeutics" (1815) he mentioned "the frequent coincidence, whether as cause or effect, between enlargement of the thyroid and cardiac disease." Reference may be made to other early cases: an anonymous writer described a clear case in 1816 (*Med.-Chir. Rev.*, vol. 1, p. 179, 1816); Stokes quoted another case from the *New England Med. Journ.* of October, 1820, and Virchow Adelman's case in 1823. Graves gave a brief account of three cases and distinguished them from ordinary goiter; but the description of "increased action of the heart and of the arteries of the neck, followed by enlargement of the thyroid gland" by W. Stokes in 1854 is so much more detailed that he really deserves the eponymic title Stokes' disease; he recorded a case in a man as well as those in women, one being sixty years of age; he mentioned a cure by iodine, quoted Sir H. Marsh's report of a necropsy in 1841, refers to the confusion with aneurysm, and stated that the first change is in the heart.

Charcot in 1859 spoke of it as "Basedow's disease," Trousseau chivalrously called it "Graves' disease" in 1860 and described the incomplete or fruste forms, and the term "Flajani's disease" was employed by his countrymen Pensuti (1887) and Gresso (1891). The eponym "Parsons' disease" is ascribed in Gould's and in Dorland's Medical Dictionaries to James Parsons (1705-1770), M.D.,



F.R.S., who received his early and classical education in Dublin, studied Medicine in Paris, received his doctorate at Rheims, and practised in London. As the disease has three other eponyms of Irish origin—Graves, Stokes, and Marsh—it seemed possible that Parsons was also a Dublin physician, but the medical historian of Ireland, Dr. T. Percy C. Kirkpatrick, Registrar of the Royal College of Physicians of Ireland, courteously informed me that there is not any evidence for this idea. So far I have failed to find the explanation for the name Parsons' disease. He was foreign Secretary of the Royal Society and contributed thirty-one papers to its *Philosophical Transactions*, but none of their titles suggests any reference to exophthalmic goiter.

The disease has more synonyms than any other disease, such as Basedow's, Flajani's, Parry's, Marsh's, Stokes', and Parsons', though the last three are very rarely employed. It is practically confined to the human race, though Bircher has produced it in dogs by implanting fresh human thymus taken from cases of Graves' disease and status lymphaticus. It has been thought to depend on a characteristic constitutional condition of a sensitive and emotional nature, which has as its anatomic basis the status lymphaticus (Moschcowitz). Enlargement of the thymus appears to have been first noticed in 1858 by Markham who recorded "Affection of the Heart, with Enlargement of the Thyroid and Thymus Glands, and Prominence of the Eyes," without mentioning exophthalmic goiter or Graves' disease, though he refers to Stokes' account. In 1850, however, H. Davies briefly reported the case of a boy aged sixteen years with a large thyroid causing dyspnea and a large thymus; but this may have been simple goiter. These observations did not attract attention for some time; Goodhart of Guy's Hospital reported a case in 1874; but Hilton Fagge (1838–1883) in his *Principles and Practice of Medicine*, which reflects on the up-to-date account of medicine in his time, merely says, "It is perhaps worthy of note that in two fatal cases at Guy's Hospital, the patients being respectively twenty-nine and twenty-one years old, the thymus was persistent." In 1893 Pierre Marie referred to the presence of a large thymus in exophthalmic goiter, cretinism, myxoedema, and acromegaly, and in 1897 Hector Mackenzie and Edmunds recorded two cases in Graves' disease with persistent thymus glands showing en-

largement of Hassall's corpuscles. Soupault described a case of definite adenomatous growth of the epithelial elements of the thymus in a case of Graves' disease, quite an exceptional occurrence. An enlarged thymus is present in about 75 per cent. of the cases, and the thyroid shows areas of lymphoid hyperplasia. This disposing constitutional condition has been regarded as being acquired as well as being congenital and hereditary (Marine, 1930). In favor of the constitutional origin of Graves' disease are Margolis' figures from postmortem examination as regards the incidence of some degree of thymic hyperplasia in forty-seven out of fifty-five cases of Graves' disease and in only sixteen out of thirty cases of toxic adenoma. It might be thought that in toxic adenoma the lymphatic condition is acquired.

Exophthalmic goiter is very uncommon in young children; among twenty-six cases (twenty-two girls) of thyrotoxicosis (twenty-one with exophthalmos) between the ages of eight and sixteen years, treated by thyroidectomy, one only was under ten years of age (Greene and Mora); of congenital Graves' disease Cockayne accepts only one case, that of Clifford White. Clark put forward the view that mongolism, first described by J. Langdon Down in 1866, is due to fetal hyperthyroidism, but the endocrine lesions described in mongolism—fibrosis of the thyroid and atrophy of the adrenal cortex and medulla—are not those of Graves' disease in an active stage, and if the thyroid fibrosis was analogous to the myxoedema sometimes following Graves' disease thyroid extract would be expected to benefit mongols, which is not the case.

That *structural changes* in the thyroid are responsible for the disease was first definitely shown by W. S. Greenfield (1846-1919), Professor of General Pathology and Clinical Medicine in the University of Edinburgh. In the Bradshaw Lecture of the Royal College of Physicians of London, delivered on November 30, 1893, and illustrated by a wealth of histologic sections, he proved in a masterly fashion by researches dating from 1883 that the thyroid shows proliferation, suggesting increased secretion, and even appears to have had a suspicion that the chemical constitution might be thus altered. Although he conscientiously mentioned a number of workers who thought that the thyroid gland might be responsible for the disease, such as Byrom Bramwell (on purely clinical grounds),

Th. Wette, Moebius, J. Renaut, A. Jeffroy, and Ch. Achard, the disease was then generally considered to be primarily of nervous origin. Osler, in his *Principles and Practice of Medicine*, in 1892, described it as of unknown origin and paid attention almost entirely to the nervous system; Bristowe did the same; Grainger Stewart and G. A. Gibson, of Edinburgh, in July, 1893, had "no hesitation in inferring it to a morbid state of the nervous system"; W. R. Gowers in the edition of his *Diseases of the Nervous System*, published in July, 1893, gave an account of it, stating that the cause was in the nervous system. Greenfield's achievement has perhaps been too readily forgotten. Almost morbidly critical of his own work, he had accumulated much new knowledge which he never published, though he gave it to his students; this he had done in the case of exophthalmic goiter, and at least from 1893 he gave all the essential features of the histology of lymphadenoma (*vide* S. McDonald) which in 1902 were independently confirmed by F. W. Andrewes, in London, and Dorothy Reed, in Baltimore. Probably the acceptance of the Bradshaw lectureship in 1893 prevented his discovery of the thyroid changes in Graves' disease from remaining hidden.

The lymphoid hyperplasia in the thyroid of Graves' disease already mentioned (p. 220) was previously pointed out by Roussy, in 1914.

Although the most obvious structural changes occur in the thyroid, doubt has been expressed as to its primary origin in that gland; it has been regarded as secondary to deficiency of the adrenal cortex and the gonads, and Marine (1930), in support of this view, quotes the case of a man who, after extensive X-ray exposures of the abdomen for a retroperitoneal growth, developed Graves' disease.

The symptoms of Graves' disease have been ascribed to an excess of normal secretion (hyperthyroidism) or to an abnormal secretion (dysthyroidism), and not infrequently cases of Graves' disease are reported under the title of hyperthyroidism by those who prefer to take a noncommittal standpoint about the occurrence of dysthyroidism; this is apt to cause some difficulty in distinguishing cases of Graves' disease from toxic adenoma, if they are really distinct. The histologic changes in the thyroid certainly favor the view that its secretion is altered in quality. Evidence has been brought forward

by H. S. Plummer that in exophthalmic goiter there are both these changes in the secretion, namely: (1) An excess in the normal secretion, which causes the symptoms of hyperthyroidism and the increased metabolic rate, and (2) an abnormal secretion resembling adrenalin in its action much more closely than it does thyroxin, and is responsible for the additional phenomena, such as exophthalmos, the characteristic nervous phenomena, and the tendency to crises that may terminate in death, present in Graves' disease but not in hyperthyroidism.

The variability in the symptoms and course of exophthalmic goiter, of which Bram, in 1929, from an experience of 4,000 cases, described twenty-six types, would be compatible with a complex origin, and the not improbable assumption that the amounts of the excessive normal secretion and of the altered secretion vary considerably in different cases. Thus, if there was an abnormal secretion only, there might well be in addition symptoms of hypothyroidism, and so a mixed picture of exophthalmic goiter and myxoedema, the latter demanding the administration of thyroid extract. This condition has long been recognized.

*Cardiovascular Symptoms.*—The pulse rate is nearly always increased, and may precede other manifestations. It is due to over-activity of the accelerator nerves and has been correlated with sympatheticotonia. The degree of the pulse rate, though largely influenced by the increased metabolic rate, cannot be regarded as an accurate index of the latter. The administration of physostigmine salicylate has been found to reduce the pulse rate and to improve the metabolic rate (Bram, 1931).

The systolic blood-pressure is usually raised to about 150 or 160 millimeters hemoglobin, and the diastolic remains about or falls below normal; but in some very toxic cases it is difficult to estimate the diastolic pressure by the auscultatory method, as a sound may be audible, as in some cases of aortic regurgitation, down to zero. The large pulse-pressure diminishes in about half the cases when the thyrotoxic state is relieved, and there does not appear to be any evidence that permanent cardiovascular changes are inevitable (Hurxthal).

The thyrotoxic heart-failure seen in Graves' disease and in toxic adenoma has been explained in various ways, such as increased

work, which undoubtedly occurs, by definite degenerative changes in the myocardium, especially fatty change (L. B. Wilson), which are not constant or permanent (H. M. Thomas), and by diminution in the amount of glycogen in the myocardium, as the result of the action of thyrotoxin. Very possibly the cause may vary in different cases. Auricular fibrillation is a well-recognized event in the course of Graves' disease, but operative treatment may be followed by the most favorable results.

*Nervous manifestations* are extremely constant and characteristic; restlessness, emotional disturbance, irritability are present and may become so prominent as to pass into mental disease. The constant state of the patient has been compared to the temporary condition of a tyro making an after-dinner speech, with the familiar palpitation, tremor, facial engorgement, sweating, and sensation of a tight collar. Muscular weakness is common and may be due to several factors, such as emaciation, cardiac inadequacy, and especially intoxication. Exceptionally paralytic phenomena have been recorded as occurring in paroxysms; Basedowian paraplegia (Charcot) and periodic paralysis (Shinosaki) resembling periodic family paralysis (Dunlap and Kepler).

*The tremor* of exophthalmic goiter, pointed out as a cardinal symptom by Pierre Marie, in 1883, is usually fine and at the rate of about ten a second, affecting the upper extremities and most obviously the fingers and even the lips and the lower limbs. It may modify the handwriting (Berg).

*Glycosuria* may or may not be present; the administration of thyroid extract normally depletes the liver of glycogen and may cause glycosuria. The combination of Graves' disease and diabetes mellitus dates from Dumontpallier's observation in 1867. The subject has been considered by Fitz, Wilder, John, and Joslin. Among 1,800 cases of diabetes mellitus, Fitz found nine of exophthalmic goiter, and among 827 cases Murphy and Moxon found eight cases, or 0.96 per cent., of hyperthyroidism. There is considerable clinical resemblance between the two conditions; Joslin refers to exchanges being necessary between clinics interested respectively in the two diseases, and both show disordered carbohydrate metabolism and independently receive benefit from insulin. The combination makes the prognosis much worse.

*Relation of exophthalmic goiter and tuberculosis.*—These two conditions have been thought to be antagonistic; Hector Mackenzie saw one case of Graves' disease in a tuberculous patient. On the other hand symptoms suggesting hyperthyroidism, especially a rapid pulse and slight enlargement of the thyroid such as commonly occurs in infections, are not uncommon in severe pulmonary tuberculosis.

*Treatment.*—Formerly intestinal putrefaction was thought to be a causal factor, and accordingly the intake of meat was forbidden or much restricted; this is not supported by clinical experience, and the diet should contain plenty of good protein. Essential medical treatment begins with rest and good feeding in order to counteract the effects of the increased metabolism. Exophthalmic-goiter patients are usually benefited, but only temporarily, by the administration of some preparation of iodine, such as Lugol's solution; iodine very probably renders the secretion of the thyroid more normal, and patients are thus enabled to undergo surgical treatment. At the Mayo Clinic the operative mortality of exophthalmic goiter was reduced from 3.5 to 0.7 per cent. Comparison of the effects of Lugol's solution of potassium iodide, both by the mouth, and of ethyl iodid inhalation, appears to show that the form and method in which iodine enters the body do not exert any influence in exophthalmic goiter; Lerman and Means also suggest that potassium iodid is preferable to Lugol's solution, which is less palatable. The response to iodine when given continuously may diminish, and a refractory phase follow with a rise in the metabolic rate (W. O. and P. K. Thompson). Graves' disease varies very markedly in its character and may be mild, severe, or very severe; many mild cases do well even under adverse conditions, and it must be agreed that spontaneous cure may occur. The methods of treatment employed have also varied very much; good results have been recorded in the different categories. X-ray treatment may undoubtedly be followed by benefit, but the formation of postirradiation adhesions is a serious handicap if subsequent operation is rendered necessary. The present tendency is to shorten the period of medical treatment before proceeding to operation. Many cases of exophthalmic goiter are cured only by operation, and Don's analysis shows that this is more uniformly successful than the alternative of X-ray exposures of the

thyroid. The position was summed up by Fraser to the effect that thyroidectomy is the most certain, but that if a surgeon with special skill and experience in the cases is not available, treatment by X-rays or by radium should be tried while the case is still mild and the patient able for work. The thyrotoxic heart of Graves' disease, which digitalis and strophanthus may fail to benefit, has been successfully treated by glucose and insulin, to correct the low sugar tolerance in this disease (Kisthinos and Gomez). Administration of an extract of the adrenal cortex (inter-renin) has been recommended on the hypothesis that the adrenal cortex controls the secretory activity of the thyroid.

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#### PRIMARY MALIGNANT DISEASE OF THE THYROID

Its occurrence as compared with other primary new growths is rather infrequent, and farther, the distinction between adenoma and early carcinoma is difficult, especially in malignant adenoma, for in this form the carcinomatous change while still inside the capsule may invade the blood-vessels and cause metastases.

Sarcoma has often been described, but some observers (Ewing, Karsner, and W. L. Smith) believe that true sarcoma primary in the thyroid has not yet been authentically established. As in the case of the prostate, carcinoma of the thyroid very seldom arises in a normal gland. As 85 to 90 per cent. of thyroid carcinomas supervene on adenoma of the thyroid, it naturally follows that thyroid carcinoma is usually found in persons coming from districts where goiter is endemic. As the risk of both toxic goiter and also of malignant change in adenomas increases with advancing age, this is an argument for thyroidectomy in all cases of adenoma (Plummer). In rare instances, carcinoma has supervened on exophthalmic goiter. It is about twice as frequent in females as in males.

The classification of thyroid carcinomas adopted by Allen Graham and Dunhill is (1) Scirrhus or simple carcinoma, comparatively rare; (2) papilliferous adenocarcinoma, which may occur in lateral aberrant thyroids in which papilliferous change is



almost universal (Dunhill) and spreads by the lymphatics; (3) malignant adenoma, or carcinoma supervening in a previous adenoma—this is much the most frequent form of thyroid carcinoma. It invades and spreads by the blood-vessels and may do this before it perforates the capsule of the adenoma.

*Bone Metastases.*—Simple goiter was formerly thought to cause secondary growths in bone [Runge (1876), Cohnheim (1876), H. Morris (1880), Warrington Haward (1882), and J. Coats (1887)]. Cases of so-called metastasizing thyroid adenoma have been recently described, for example, by Euzière, Viallefont, and Bert, in 1930. This interpretation of the malignant process may be explained by a microscopic resemblance of the metastases to normal thyroid tissue. But this paradoxical conception of “benign metastasizing goiter” has ceased to carry conviction; Simpson’s analysis of seventy-seven reported cases showed that histologic examination was carried out in twenty-nine only; among these cases the secondary growths were most often in the skull, vertebrae, and pelvis. The metastases may occur while the malignant nature of the primary thyroid growth is unsuspected, as the enlargement is slight. It appears that, like a few cases of primary carcinoma of the liver which contain bile (Perles, Paul, Cloin, Ribbert, F. P. Weber), may be functionally active, and even compensate for thyroid insufficiency; von Eiselsberg reported a case of total thyroidectomy by Billroth followed by myxoedema which disappeared when a metastasis appeared in the sternum; five years later the sternal growth, which contained colloid material, was removed and myxoedema recurred. Bony growths may pulsate and vary in size, but are comparatively chronic. As a cause of secondary growths in the skeleton thyroid carcinoma has been regarded as the most important after mammary carcinoma and, according to Ewing, the prostate.

Renal hypernephromas are also well known to cause secondary deposits in bone; but the hypothesis of Grawitz that they arise in suprarenal “rests” in the kidney no longer holds the field, these tumors being derived from renal epithelium; hence any association between the thyroid and adrenal cortex as normally influencing bodily growth on the one hand and the tendency of malignant disease of those glands and bony metastases now falls to the ground.

*The symptoms* of malignant disease of the thyroid, it may be

noted, are mainly those of malignant disease and not those of want of thyroid secretion. This is paralleled by the absence, or at best extreme rarity, of the manifestations of Addison's disease in malignant tumors of the adrenals.

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## RIEDEL'S THYROIDITIS

In 1896, Riedel described a dense fibrosis of the thyroid gland which has received other names, such as iron struma, chronic ligneous thyroiditis, and benign granuloma of the thyroid. It is rare; in 1926, Smith and Clute collected thirty-five cases by fifteen authors and added five, forty in all. It occurs more often in women (thirty out of forty cases) and at about the fourth decade. In 1912, Hashimoto described a condition of extensive lymphoid invasion of the thyroid, which he considered was distinct from Riedel's thyroiditis. Ewing, however, regards it as the early stage of that condition.

The thyroid gland becomes adherent to the adjacent tissues of the neck, but not to the skin, and the borders of the gland thus become rather indefinite. The densely fibrosed gland compresses and narrows the trachea, causing dyspnea, and in a few cases the

esophagus, causing dysphagia. Symptoms of myxoedema do not occur, except after complete thyroidectomy. It may be regarded clinically as a malignant disease, and it is possible that some of the cases reported as sarcoma, on histologic examination, are really thyroiditis. In 1911, Delore and Alamartine spoke of X-ray exposures as an almost specific remedy, but the only efficient method of treatment is surgical.

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#### THE PARATHYROID GLANDS

Though Richard Owen (1862) and Virchow (1863) observed what were probably parathyroid glands, the first real anatomic account of them was given in 1880 by Ivar Sandström, who regarded them as "embryonic rests" of thyroid tissue. Baber, in the following year, described them as undeveloped portions of the thyroid gland. Kohn, in his description of "epithelial bodies" in 1895, was one of the first to controvert the view that the parathyroids are parts of the thyroid, and in 1898 D. A. Welsh followed his example. It is historically interesting to refer to Dunhill's frank and independent paper, published as recently as 1924, which shows first the mental attitude of surgeons who, having performed many thyroidectomies without the complication of tetany, were somewhat sceptical about the parathyroids. Then Dunhill, who had shared this feeling, investigated for himself the anatomic position and structure of the parathyroids, and by dissections in the postmortem room found that he could demonstrate them with precision.

The parathyroids, which must be distinguished from accessory thyroid and small lymphatic glands, are usually four in number, though the number varies. They lie along the inner border of the lateral lobes of the thyroid gland, two on each side, the lower near the entrance of the inferior thyroid artery into the thyroid gland being the larger. With regard to the question whether or not they

are ever included within the thyroid gland, a point of importance in connection with tetany after thyroidectomy and the possible parathyroid origin of some carcinomas of the thyroid, opinions differ; Getzowa, Erdheim and Forsyth state that these inclusions occur; W. G. MacCallum has not observed it, and Dunhill said that all the parathyroids in man are outside the capsule of the thyroid gland: "This is fortunate for the surgeon—and the patient!" In the living body they are of a dark terra cotta color.

For some years after Sandström's description the parathyroids did not attract attention from physiologists, or, indeed, generally; thus there is not any heading of parathyroid glands in the index catalog of the Surgeon General's Library at Washington in the edition of 1889. In 1892, after Gley, as the result of experimental removal of the thyroid and the parathyroids produced fatal tetany, removal of the parathyroids alone being without any bad effect, he concluded that the parathyroids supplement the function of the thyroid and are of importance only when the thyroid has been removed. This view was soon contested, especially by Vassale and Generali, who found that the functions of the two glands were quite distinct, the thyroid supplying an internal secretion, the absence of which was followed by myxoedema, the parathyroids exerting an antitoxic function, failure of which resulted in tetany. In 1908-1909, W. G. MacCallum and Voegtlin investigated experimentally the relation of the parathyroids to calcium metabolism and tetany by extirpating the parathyroids in dogs. They showed that the parathyroids control calcium metabolism, that inadequacy or parathyroidectomy leads to a toxemia which causes excessive excretion of calcium, that the brains of parathyroidectomized animals contain only half of the normal amount of calcium, and that deficiency of calcium causes the hyperexcitability of the central nervous system, and so, tetany. Noel Paton and his co-workers, in 1916, brought forward evidence to show that the poison responsible was guanidine and it was suggested that the parathyroids prevent the formation of guanidine by means of a ferment (Vines). It would be interesting to know if the arterial blood-pressure is raised in tetany, for Major and his co-workers ascribed high blood-pressure to an increased blood content of guanidine compounds. As bearing on the suggestion that the parathyroids remove guanidine from the blood, it may be men-

tioned that Altnow and O'Hare gave parathyroid extract to three hypertensive patients without any effect on the blood-pressure.

From an analysis of thirty-eight cases in which the parathyroids were completely or partially removed, the results fell into two categories: (1) Alteration in the calcium and phosphate content of the blood-serum associated with tetany, and (2) cataract, brittleness of the nails, loss of hair, and decay of the teeth (Cole). The administration of Collip's parathyroid hormone (parathormone) causes hypercalcemia and its physiologic effects of dryness of the upper respiratory tract, warmth and tingling of the skin, increased strength, and constipation. In dogs, loss of appetite, vomiting, diarrhea, weakness, drowsiness, and circulatory failure have been observed by Collip. Halsted, in 1909, showed experimentally that grafting of the parathyroids could be successfully carried out.

*Applications in Treatment.*—Just as thyroid extract was at one time advocated as a panacea, so has parathyroid been recommended for many of the ills to which flesh is heir. As an explanation of the successive phases of a remedy's reputation—a universal cure—all when new, then discredited, and finally attaining its real position—it has been suggested that at first all the easily suggestible people take it and, convinced that it will do them good, they get better; then when it is taken by ordinary non-impressionable people the factor of autosuggestion is inactive and the remedy loses its early reputation (J. J. Walsh). As the parathyroids have been regarded as antagonistic to the thyroid, it is curious to recall that both of them have been recommended as beneficial for prostatic enlargement. It has also been reported as successful in asthma, urticaria, plumbism, sprue, chronic infections (H. W. C. Vines), ulcerative colitis, ulcers, especially in the hemoptysis of pulmonary tuberculosis, the patients experiencing general improvement, and in combination with calcium in jaundiced patients before operation to prevent hemorrhage (Gordon and Cantarow). Parathyroid therapy was not in a satisfactory position until in 1925 Collip introduced a reliable preparation ("parathormone").

In chronic lead poisoning the bones contain much of the metal, and it has been found that Collip's parathormone mobilizes the lead as well as the calcium and so is followed by increased excretion of lead (Hunter and Aub). In like manner it has been successfully

employed by injection to remove radium and thorium from the bones of girls employed in painting luminous clock dials in America, who from constantly pointing with their lips the brushes with a paint containing these radio-active bodies suffered from radium poisoning (Flinn and Seidlin). Parathyroid extract and calcium were strongly recommended in sprue by H. H. Scott some years ago, but the results of this treatment have not come up to these expectations; Carmichael Low, for example, by comparison of two control series, concluded that no special benefit could be ascribed to it.

*The Parathyroid and Changes in Bone.*—Just as the therapeutic use of insulin was followed by the recognition of hypoglycemia from excessive doses and later by the realization that spontaneous hypoglycemia may be caused by hyperplasia, adenoma, or carcinoma of the islands of Langerhans and the resulting hyperinsulinism, so the use of parathyroid hormone has made the effects of hyperparathyroidism in decalcification of bone more familiar. According to Donald Hunter more than a hundred cases of bone disease associated with hyperplasia or tumor of the parathyroids have been reported since 1907 when Erdheim reported parathyroid enlargement in osteomalacia.

There are two interpretations of the association of bony and parathyroid changes. It was thought by Erdheim that the parathyroid hyperplasia is secondary and compensatory to the disturbance in calcium metabolism caused by lesions in the bones, for example, in carcinomatous metastases and multiple myelomas. Such secondary changes should be found in all the parathyroids, and when one only of the four parathyroids is enlarged the probabilities are that it is an adenoma rather than hyperplasia, though the line dividing these two conditions is thin, and that it is the primary lesion and so responsible for the bony changes. According to Hoffheinz 85 per cent. of the recorded parathyroid tumors have been single.

*Tumors* of the parathyroid glands were first described as fetal adenomas of the thyroid (Wölfler), and then as "glycogenic tumors" (Kocher). The parathyroid origin appears to have been first realized by De Santi. The parathyromas may, like the parathyroids, be either embedded in the thyroid (the "fetal adenomas") or be

juxtathyroid, lying external to that gland; out of twenty-nine parathyroid tumors sixteen were intrathyroid (parastrumas) and thirteen extrathyroid (Berard and Alamartine); the former must in the past have been regarded as thyroid adenomas. The parathyromas are prone to contain much glycogen, and may contain thyroid tissue (five out of twenty-nine) as well as cells of the parathyroid type; they may be innocent or malignant.

Parathyroid tumors may occur without any bony changes; among eighty-eight tumors collected by Ask-Upmark there were forty-nine cases with bony lesions (thirty-nine osteitis fibrosa cystica and ten osteo-malacia). It is noteworthy that some of the parathyroid tumors unaccompanied by bony lesions have been very large, the size of a child's head. Bland-Sutton recorded one which compressed the trachea with fatal results. The association of parathyroid tumor with osteitis fibrosa cystica was first pointed out by Askanazy in 1904, and is the most satisfactory instance of the parathyroid origin of bone disease; nearly all the cases of osteitis fibrosa cystica present a parathyroid tumor, and this condition has been shown not to be improved by the administration of the parathyroid hormone (Mandl).

In 1891 von Recklinghausen described "tumor-building osteitis deformans," which seems to be identical with, or closely allied to, generalized osteitis fibrosa cystica. It more often attacks females than males, and usually between the ages of thirty and fifty-five. The clinical manifestations are bony softening, deformities, local bony projections, fractures, muscular weakness, pain, hypercalcemia, and increased excretion of calcium in the urine. Skiagraphy may show cysts in the bones. It must be distinguished from Paget's osteitis deformans which is not accompanied by parathyroid tumors. An overactive parathyroid tumor, such as an adenoma or carcinoma, may exist and cause osteitis fibrosa cystica without being palpable in the neck; in nine out of fourteen cases collected by Donald Hunter in December, 1929, the tumor present could not be felt before operation, but on exploration a parathyroid tumor was found in all except two of the cases. The only satisfactory treatment so far practised is surgical removal of the parathyroid tumor. Whether or not X-radiation has been employed for this purpose I do not know; but symptoms of tetany have followed irradiation of the thyroid in Graves' disease.

employed by injection to remove radium and thorium from the bones of girls employed in painting luminous clock dials in America, who from constantly pointing with their lips the brushes with a paint containing these radio-active bodies suffered from radium poisoning (Flinn and Seidlin). Parathyroid extract and calcium were strongly recommended in sprue by H. H. Scott some years ago, but the results of this treatment have not come up to these expectations; Carmichael Low, for example, by comparison of two control series, concluded that no special benefit could be ascribed to it.

*The Parathyroid and Changes in Bone.*—Just as the therapeutic use of insulin was followed by the recognition of hypoglycemia from excessive doses and later by the realization that spontaneous hypoglycemia may be caused by hyperplasia, adenoma, or carcinoma of the islands of Langerhans and the resulting hyperinsulinism, so the use of parathyroid hormone has made the effects of hyperparathyroidism in decalcification of bone more familiar. According to Donald Hunter more than a hundred cases of bone disease associated with hyperplasia or tumor of the parathyroids have been reported since 1907 when Erdheim reported parathyroid enlargement in osteomalacia.

There are two interpretations of the association of bony and parathyroid changes. It was thought by Erdheim that the parathyroid hyperplasia is secondary and compensatory to the disturbance in calcium metabolism caused by lesions in the bones, for example, in carcinomatous metastases and multiple myelomas. Such secondary changes should be found in all the parathyroids, and when one only of the four parathyroids is enlarged the probabilities are that it is an adenoma rather than hyperplasia, though the line dividing these two conditions is thin, and that it is the primary lesion and so responsible for the bony changes. According to Hoffheinz 85 per cent. of the recorded parathyroid tumors have been single.

*Tumors* of the parathyroid glands were first described as fetal adenomas of the thyroid (Wölfler), and then as "glycogenic tumors" (Kocher). The parathyroid origin appears to have been first realized by De Santi. The parathyromas may, like the parathyroids, be either embedded in the thyroid (the "fetal adenomas") or be



# Surgery

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## A USEFUL PROCEDURE TO FACILITATE BRINGING TOGETHER THE FRAGMENTS OF A FRACTURED PATELLA OF LONG STANDING\*

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THE best results in the operative treatment of fractured patella are secured when the operation is performed as soon as is reasonably possible after the injury is received. I have demonstrated within the last few years in approximately twenty cases that in those cases in which the operation is performed within the first day or two after injury, the healing is prompt and the joint function is only briefly and slightly impaired.

There are cases, however, in which for one reason or another it is not wise to perform the operation for several weeks after the occurrence of the fracture. Every surgeon knows the difficulty experienced in such cases of bringing the bone fragments into contact so that they may be retained by sutures. A recent case under my care was of this type. In addition to the fractured patella the man had suffered also an injury to the skull, a serious injury to the liver, and a fractured pelvis. On account of the liver injury, the man was desperately sick for a number of days and it was nearly a month before it seemed advisable to operate on the patella.

A curved, transverse incision with the convexity upward was made about two inches above the patella, the skin was dissected up and resected downward, until the tear in the capsule was reached, and the fragments of the broken bone were well exposed. It was found that the upper fragment of the patella had been pulled two or three inches away from the lower fragment, and was not easily brought down to contact. It occurred to me during the operation to

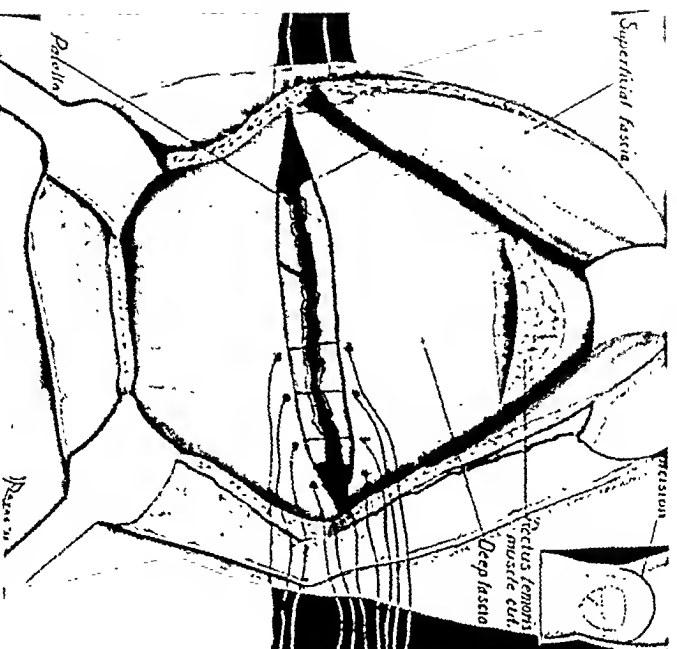
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\* From the Department of Surgery of the Medical College of Virginia.

make a transverse incision across the lower fibrous portion of the rectus femoris muscle, and when this was done, the upper fragment was easily pulled down with good contact with the lower fragment, and sutures were placed without tension. X-ray pictures taken before and after the operation are shown in the accompanying illustrations. (Figs. 1-4)

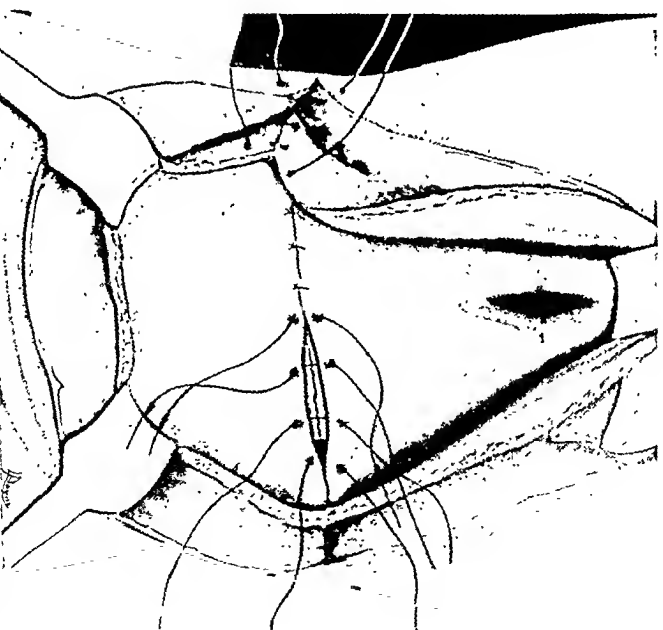
The method is not new in principle, and there have been devised other plastic measures designed to secure the same effect. However, this simple little procedure was adequate.

FIG. 1.



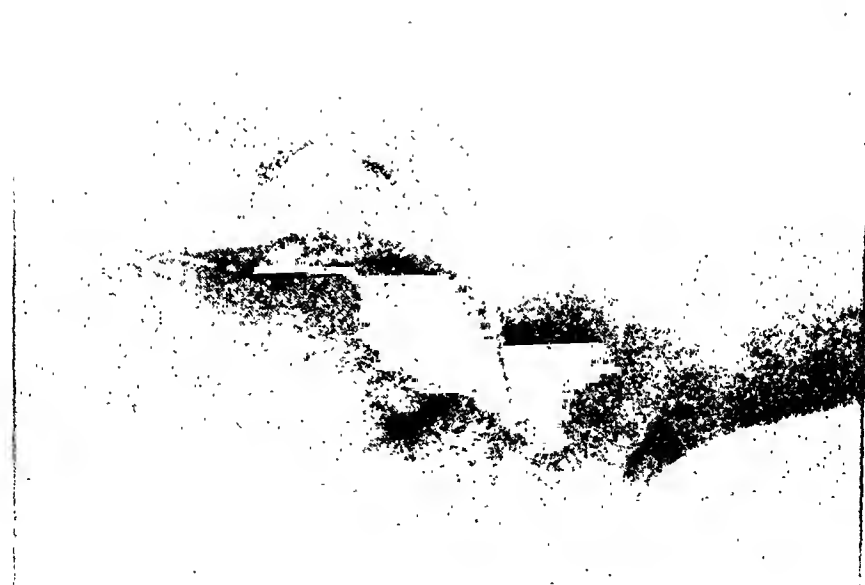
Showing the incision made in the lower portion of the rectus femoris muscle and the capsule of the joint being sutured.

FIG. 2.



The patella is pulled down, making the transverse incision in the rectus femoris in a longitudinal direction, bringing the bone fragments into close apposition and relieving tension on the sutured line of the capsule. The superficial fascia is being sutured.

FIG. 3.



Skagraph of fractured patella before operation.

FIG. 4.



Skagraph of fractured patella after operation.

## TORSION OF THE TESTIS\*

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Torsion of the testicle, or better called, torsion of the spermatic cord, is a condition caused by a sudden twist of the spermatic cord, shutting off the blood supply of the testicle and epididymis; causing alarming symptoms of excruciating pain in the involved testicle; swelling of the affected side; at times generalized symptoms of shock, nausea and vomiting and in some instances fever and prostration; and if not relieved instantly by untwisting the cord through an open operation, aseptic gangrene ensues, leading to complete atrophy of both testicle and epididymis.

Torsion of the testicle was considered to be very rare, but since attention was called to this condition in the literature, more reports are appearing every year. The main reason for the scarcity of cases is that many cases of probable torsion were either taken to be traumatic epididymitis, treated medically and never operated upon, or—the cases were operated upon very late, after atrophy and complete destruction had taken place, where the actual cause of this gangrene had either been overlooked or the pathology so changed as not to enable one to ascertain the primary cause of the destruction.

We report here a case of torsion of the testicle operated upon eighteen hours after onset.

No. 62959. J. B. Aged 24. Admitted to the Urological Service of the Mt. Sinai Hospital on April 24, 1931 complaining of severe pain in his left testicle. The patient, a clerk in a grocery store, stated that about six o'clock the previous evening, after lifting heavy cakes of Swiss cheese, he experienced some pain in his left testicle. He kept on working for several hours, but finally had to stop, because of the pain becoming more acute and severe. He spent a sleepless night, suffering excruciating pains without relief. During the morning hours the pain became unbearable and he came to the hospital. The examination revealed the patient to be a healthy, but thin individual, with no other complaints than terrific pain in the left testicle. Physical examination was absolutely negative, except for the scrotal condition. The right side of the scrotum appeared normal; the left side was red, swollen about three times the normal size, and highly

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\* From the Urological Service of the Mt. Sinai Hospital, Philadelphia, (Chief Dr. Alexander Randall).

tender to touch. On palpation a rounded mass, the size of an orange, was palpable through the edematous scrotal wall, freely movable like a simple hydrocele. The mass did not transmit light. The rectal examination revealed normal findings. Diagnosis of torsion of the testicle was made and immediate operation advised.

*Operation.*—Incision was made over the left side of the scrotum, exposing a darkened tunica vaginalis, very tense, filled with a dark bloody serum. The inner wall of the tunica vaginalis was somewhat bluish in color with multiple petechia all over the surface. The testicle with the adjacent epididymis was floating freely in the sac, and hanging by its cord, like a tongue in a bell. The testicle and epididymis were bluish-violet in color very tense and about one and one-half times the size of normal. The spermatic cord, on which the testicle was suspended in the vaginal sac, showed two twists, cutting off the blood supply of the testis and epididymis. It was impossible to untwist the cord, each turn of the cord having produced already an imprint on the one below, held in place by force. Orchidectomy was performed. The wound closed with catgut about a drain of rubber dam. The patient made an uneventful recovery, leaving the hospital on April 29, 1931.

*Pathological Report.*—The specimen (see colored frontispiece) consists of a testicle with its adnexa. Both testicle and epididymis, the spermatic cord and tunica vaginalis are bluish-violet in color, hard in consistency covered by a shiny tunia. The spermatic cord shows two twists intravaginally, firmly held in position when untwisting is attempted. Both testicle and epididymis do not have any connection with the walls of the vaginal sac, the covering of the tunica, tests and epididymis being glossy and smooth throughout. The only attachment between the tunica and the contents of the sac is around the spermatic cord above the twists. The testicle and the epididymis both hang in the vaginal sac like the heart in the pericardial sac. The epididymis is closely attached to the testicle, appearing normally formed.

*Comment.*—The features of this case are numerous. The early diagnosis, early operation, the double twist of the spermatic cord, the intravaginal location of the twist, the freely "floating testicle," and the force which held the cord twisted, making untwisting impossible.

*Incidence.*—O'Connor (1919) collected 124 cases from the literature both American and foreign and added two of his own. Since then many others have added cases. *Baudet* (1922) one case, *Barney* (1922) one, *Keyes, Collings and Campbell* (1923) seven, *Brady* (1923) three, *Griffin* (1923) one, *Weitz* (1923) one, *Iselin* (1924) one, *Gilberti* (1924) one, *Massa* (1925) one, *Petridis* (1925) one, *Martin* (1926) one, *Fullerton* (1926) two, *Corti* (1926) one, *Gibson* (1926) two, *Meltzer* (1926) one, *Irk* (1926) one, *Kummer* (1926) one, *Marconi* (1926) one, *Campbell* (1927) eight, *Perard* and *Arriset* (1928) two, *Johnson* (1929) one, *Segato* (1929) one,

Birdsall (1930) four, *Whitemore and Zweibel* (1930) one, *Rocher and Guerin* (1930) one, *Petrignani* (1930) one, *Lahayville* (1930) one. The total cases being 194.

*Etiology.*—It is said that torsion cannot occur with the normal testicle, some congenital anomaly or defect must be present. In addition to this antecedent pathology a force is necessary in order to twist the spermatic cord around its axis.

O'Connor states in his review of 124 cases from the literature, that seventy-two of the cases were incompletely descended testes and fifty-two showed normal position. Seventy-five per cent. of the cases occurred in men under twenty years of age.

Meltzer mentions nine abnormalities encountered in reviewing a large number of torsion cases from the literature.

1. A very roomy tunica vaginalis extending all the way up the cord.

2. An open tunica vaginalis.

3. Absence of the gubernaculum testis and posterior mesorchium.

4. Absence of scrotal ligament.

5. Abnormal attachment of the common mesentery and vessels to the lower pole of the testis and to the globus minor, so that the testis is attached by a narrow stalk, instead of a broad band. (*Meltzer's case.*)

6. Elongation of the globus minor.

7. Excessive length and poorly attached intravaginal spermatic cord.

8. When the connections between the testis and epididymis are very loose and mobile.

9. When the connection between the scrotal contents and the tunica are very loose and mobile. In an extreme case this situation is very marked, the testis with the epididymis may hang freely in the vaginal cavity, like a tongue in a bell. (Our case) "*Floating testis*" (*Lauenstein*).

The torsion might occur either outside of the tunical sac or inside of it, thus giving an intravaginal or extravaginal torsion. In the case of an extravaginal torsion the entire testicular mass, including testis, epididymis and tunis, will rotate within the scrotum. In such an instance we must preclude the absence of attachment between the

outer surface of the vaginal sac and the inner wall of the dartos, permitting free movement of the whole sac, in toto. Such a situation is usually encountered in cases of imperfect descensus of the testis, the sac being either loosely attached or forced down from a higher position without having time to form new attachments.

The intravaginal torsion is more frequent, the twist of the spermatic cord occurring within the vaginal sac. In such a case the testicle must have been freely movable within the cavity.

In both instances we must admit the existence of a force that was strong enough to rotate the abnormally situated testicle and its adnexa. It is generally being admitted, now, that this force is produced by the cremaster muscle. A violent contraction of this muscle might dislocate and turn a movable testis.

Many a patient admits unusual mobility of the testis prior to the torsion, especially in partially descended cases or in congenital hydroceles. *Van der Poel* reports a case, where the patient learned to untwist his own cord. *Bardy* states that in cases with open tunica vaginalis, the whole cord can be twisted in its entire length.

*Symptoms.*—The acute torsion of the testicle is characterized by a sudden onset usually after heavy lifting or straining, but can also occur during sleep, probably due to some unnoticed twisting and pressure. There is an early swelling and acute pain. At times generalized symptoms occur: nausea, vomiting, chills, fever, and abdominal pains. In some cases the pain may not be severe at first, gradually in severity and local inflammation.

*DIAGNOSIS.*—Antecedent mobility, incomplete descension, muscular strain, sudden onset during sleep and absence of venereal history should make one consider the possibility of torsion of the testis. Especially the absence of venereal history and sudden onset with excruciating pain will always help in establishing the diagnosis, because the first possibility thought of is acute epididymitis, which can easily be eliminated from the history of the patient.

The other condition which can simulate torsion is incarcerated hernia, but a careful examination will reveal the true nature of the condition present. The history and general symptoms produced and a careful local examination will indicate whether or not a hernia is present. There are though cases reported where it was impossible



to arrive at a definite diagnosis and the same was made only after opening of the sac.

*Pathology.*—In either case of extravaginal or intravaginal torsion, there is no possibility of colateral circulation. The torsion closes the veins completely, while the arteries are still partially open, permitting the pumping in of more blood, and causing a hemorrhagic infarct of the scrotal contents. Soon aseptic necrosis sets in due to lack of circulation, with the final atrophy of the organs involved. In some instances, infection brought into by the blood-stream causes a suppuration of the scrotal contents, leading to abscess formation.

*Treatment.*—Several authors succeeded in untwisting the cord and establishing a normal circulation. *Campbell* reports three cases in which he was able to establish circulation by untwisting the cord. *Lahayville* reports untwisting or "detorsion" of the cord in a case operated upon very early; he followed the case up and found one year later complete atrophy of the testis. *Nash* operated on his case one hour after onset, untwisting the cord, establishing apparently good circulation, but his case also went into complete atrophy. All the authors agree, that in very early cases an attempt should be made to untwist the cord, but as it happened in our case, this frequently is impossible to accomplish, the twists being very tight and held firmly in place.

After the cord is untwisted, orchidopexy should be done, suturing the testis to the bottom of the scrotum, performing also a hydrocele operation in order to form lateral and lower adhesions, to hold the testicle in place. When the untwisting is impossible or the case is operated upon late, orchidectomy is the only choice. *Keyes* suggests a prophylactic operation upon the healthy testicle at the same sitting, performing orchidopexy and inversion of the tunica to prevent future. Unwinding the twist in an unexposed testis is considered dangerous, being a blind procedure, especially since the direction of the twist is unknown.

*Experimental Work.*—*Keyes, Collings and Campbell* succeeded in reproducing torsion of the testis in the dog. They operated upon five dogs, twisting the cord  $360^{\circ}$  and in others  $540^{\circ}$  anchoring the lower pole of the testis. They invariably obtained gangrene of the scrotal contents forty-eight hours after the experimental torsion. Three weeks later all organs showed complete atrophy.

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# USE AND ABUSE OF THERAPEUTIC INHALATIONS OF OXYGEN\*

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IN ORDER intelligently to employ oxygen by inhalation it is necessary to know what we may accomplish by its use. The understanding of the mechanism of oxygen utilization is a matter of comparatively recent development. Knowledge of the blood gases is the result of work of men who are still living. Until the studies of Haldane, Barcroft, Lundsgaard, and Van Slyke, were available, a really intelligent use of oxygen was not developed.

Barcroft is responsible for the division of oxygen want or anoxia into three categories: anoxic anoxia, due to incomplete oxygenation of the hemoglobin in the arterial blood; anemic anoxia, when there is a deficit of hemoglobin capable of carrying oxygen; and stagnant anoxia, due to the slow passage of blood through the tissues. To these, Peters and Van Slyke have added a fourth division, histotoxic anoxia, due to the inability of tissue cells to utilize oxygen because they have been poisoned as by cyanide, alcohol, and certain other narcotics.

The collection of knowledge concerning oxygen want was stimulated during and after the World War by the studies in connection with aviation and in attempts to alleviate the results of gas poisoning. Submarine and tunnel engineering have also contributed.

At the present time, the following symptoms are regarded as those of acute anoxia: central nervous disturbance, hyperpnea, weakness, collapse, with or without cardiac syncope. In the stagnant varieties of anoxia, there may develop symptoms of shock and circulatory failure.

Lundsgaard has carefully studied the symptoms accompanying acute anoxias of various degree. As summarized by Peters and Van

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\* From the Littauer Pneumonia Research Fund of New York University and the Medical Service, Harlem Hospital, New York City.

Slyke from the studies of Y. Henderson and his co-workers, the different degrees of anoxias present the following symptoms:

*Effects on Resting Normal Subjects of Acute Anoxias of Varying Intensity*

Degree of Anoxia	Saturation of Arterial Hb.	Symptoms
First degree..... First obvious signs.	89% to 85%	Accelerated pulse and respiration. More than usual effort required for mental concentration. Muscular coördination of finer-skilled movements somewhat disturbed.
Second degree..... Pre-coma or post-coma. Encountered either before unconsciousness or after recovery from short period of it.	87% to 74%	Judgment faulty. Emotions, such as hilarity and pugnacity, easily roused and unstable. Staggering gait. Muscular effort causes quick fatigue and may injure heart. Fainting may occur. Bruises, cuts, burns may not be felt. Typical of alcoholic intoxication. Man recovering from asphyxia is not responsible.
Third degree..... Coma.	74% to 33%	Subject becomes unconscious. If in fit physical condition coma is cerebral with "rigid, glassy-eyed" unconsciousness, almost instantly terminated by O <sub>2</sub> inspirations. If less fit, cardiac syncope occurs before cerebral. Dazed mental state prevents realization of danger as coma comes on.
Fourth degree..... Exitus.	74%	Coma—respiration reduced to gasps—respiration stops—6 to 8 minutes later heart stops.

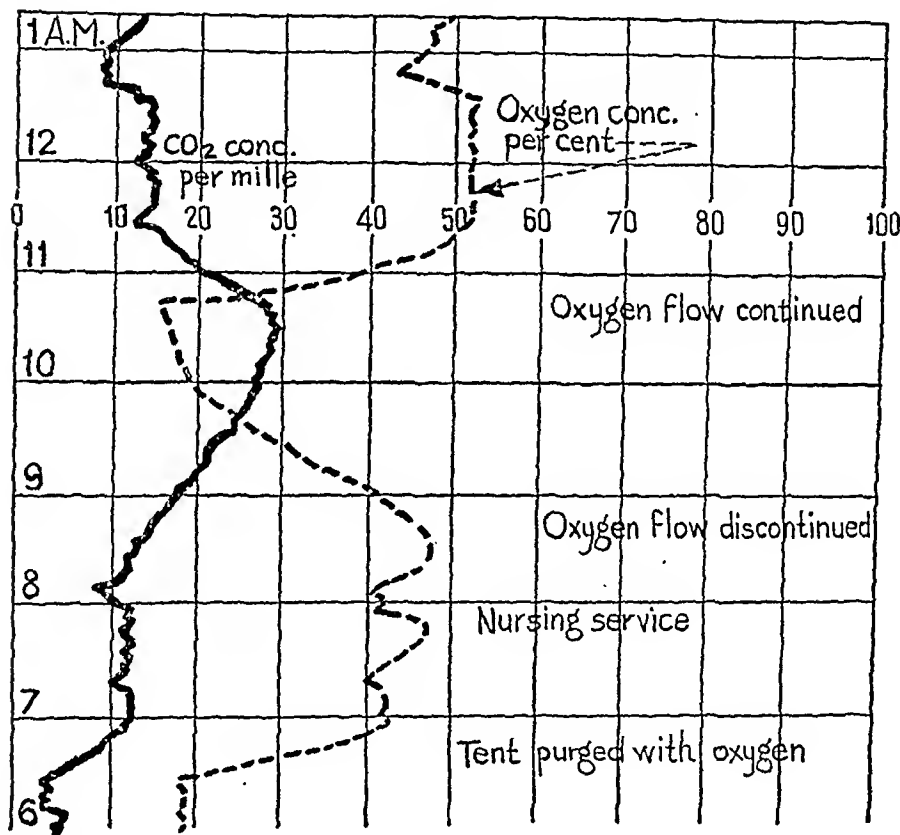
When patients are in a normal atmosphere at sea level, they breathe air containing almost 21 per cent. of oxygen. In the alveoli of the lungs the air meets venous blood containing only 13 volumes per cent. of oxygen (volumes of gas, reduced to standard conditions, contained in 100 volumes of blood). Oxygen diffuses into the blood until the blood contains 19.5 volumes per cent., in which state it is about 96 per cent. saturated. The air in the alveoli has become impoverished of oxygen so that it leaves with only 14.8 volumes per

cent. oxygen. More oxygen might be extracted from the air but not much, and only slowly since the oxygen in air and in blood are almost in equilibrium. Full saturation does not occur because the blood does not remain in the alveolar capillaries long enough to permit it.

Fresh air must have access to the venous blood; in disease,

CHART I.

## HARLEM HOSPITAL OXYGEN TENT



obstructions may occur at various levels in the airways. Oxygen will prove helpful in mechanical obstructions by permitting less frequent renewal of alveolar air.

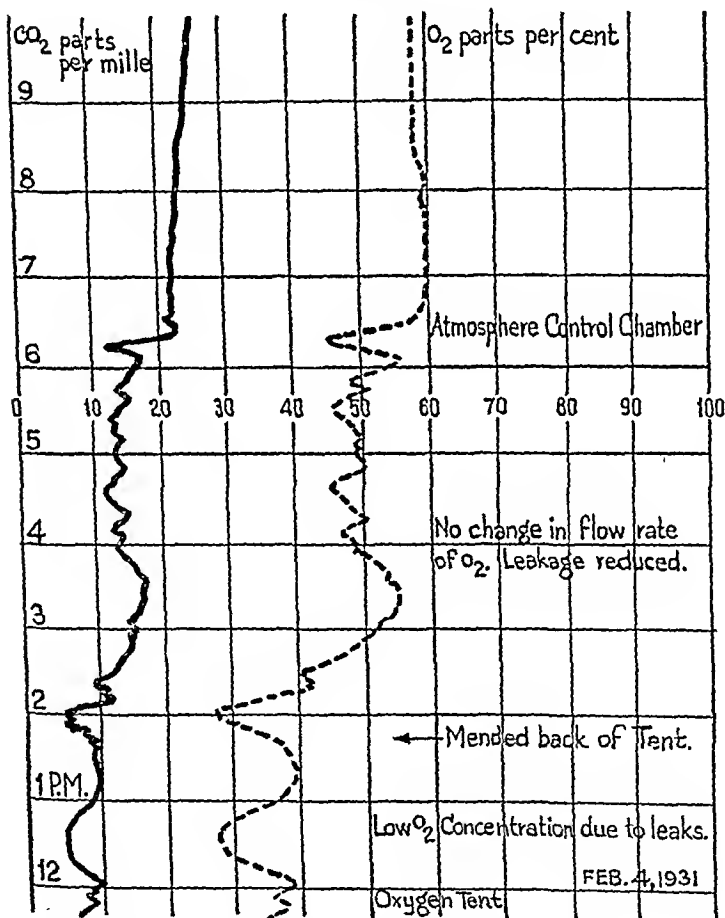
If, for any reason, some of the alveolar capillaries become wholly or partially closed to the flow of blood, or the diffusion of oxygen through the alveolar epithelium is retarded, the total amount of venous blood will not be re-oxygenated to about 95 per cent. of its full capacity, and anoxic anoxia will be present.



The degree of relief afforded by inhalation of oxygen-enriched air depends in part upon the mechanism of the respiratory obstruction.

CHART II.

HARLEM HOSPITAL  
Oxygen and Carbon Dioxide Concentration  
Atmosphere Control Chamber  
and Tent



tion. If the cause is a reduction in the diffusion rate of oxygen into the capillaries, due to effusion or inflammation of the alveolar epithelium, oxygen inhalations are indicated to restore the diffusion rate by increasing the concentration gradient of the diffusing oxygen.

in the alveoli, an oxygen saturation of the arterial blood of 56 per cent. may be overcome by raising the oxygen tension in the inspired air to 26 per cent.

There are numerous clinical reports of the value of oxygen in relieving the severe grades of anoxia, and also of the danger of even a moderately severe condition of oxygen want. Stadie, in his study of the effect of oxygen want on pneumonia, found that when the oxygen saturation was less than 86 per cent. in the arterial blood, the prognosis became bad. This work has been confirmed by other observers.

Cyanosis, which was formerly given as the criterion for the use of oxygen, is obviously not the earliest symptom of want. On our own service at Harlem Hospital, we regard a pulse above 120, and a doubled respiration rate, or thirty-six per minute, as an indication for oxygen administration in pneumonia or acute respiratory infections. The first response to oxygen want is increased pulse and respiratory rate, with feelings of discomfort and lack of muscular coördination. When cyanosis does supervene, it may mean that alveolar capillaries are closed, some of the blood passing through unaërated channels is mixing with the aërated blood, or that there has developed a polycythemia in response to the anoxemia or that the circulation and central nervous system have commenced to fail and that stagnant anoxia has been added to the obstruction in the lungs. Accordingly, it is unwise to wait for the occurrence of cyanosis to administer oxygen when other earlier symptoms of oxygen want are present. Oxygen want should be recognized before cyanosis appears. Cyanosis may be absent when the patient is anemic, or poisoned with carbon dioxide, and defensive mechanisms, increased rate of breathing, may temporarily delay its appearance.

As long as oxygen was a costly drug and obtained by chemical breaking down of perchlorates or permanganates, its medical use was restricted by the expense of manufacture and purification. The introduction of the liquid air distillation and electrolytic methods of oxygen manufacture for utilization on a large scale in furnaces, for welding and other industrial purposes, has made oxygen clinically available and has advanced the practice of its utilization. Oxygen prepared for industrial purposes can be safely used in medicine. The traces of gas which dilute it are normally present in the atmos-

pherc. There is no purpose in preserving the fetish of "medical oxygen" which survives from the time when the oxygen taken from the chlorates was especially washed.

From what has been said, it is obvious that unless oxygen is given in sufficient concentration to increase the head with which it diffuses into the blood, slight effect can be expected. On this account, the methods for administering oxygen deserve discussion. Furthermore, when it is realized that oxygen diffuses into the blood-stream and is rapidly utilized, the futility of intermittent administration can be appreciated. To give oxygen until cyanosis disappears, and then to wait until it reappears, does not seem a rational therapeutic procedure. The only circumstances under which such a procedure might be justified is when no equipment for continuous administration is available, or when high concentrations are desirable to overcome cyanosis and then the hope is sustained that by intermittent use the destructive effects of such high concentrations may be obviated. This is the usual procedure when oxygen is administered by inhalation with the Haldane mask.

There are six methods of oxygen administration by inhalation:

1. Funnel.
2. Mask.
3. Nasal inhaler.
4. Catheter.
5. Tent.
6. Chamber, portable or stationary.

The funnel method is mentioned to be condemned. If the funnel is held close over the nose and mouth, it becomes in effect a mask. If it is held further away the concentrations in the pharynx are little influenced and the oxygen gradient between the outside air and the blood-stream is little affected. It requires the constant care of an attendant and has the further disadvantage, when closely applied, of obstructing the breathing and that oxygen of unknown concentrations is inhaled. (See Fig. 1.)

The Haldane mask permits of some re-breathing. High concentrations of oxygen are possible and there is a building up of the carbon dioxide; this, when it passes 3 to 5 per cent. increases the depth of respiration. The mask must be used intermittently in order that prolonged high concentrations of oxygen (over 70 per

cent.) are not kept in contact with the alveolar epithelium. By its use, cyanosis may disappear and the patient may be benefited. However, this method requires the constant watchful care of a nurse lest the patient become cyanosed and anoxemic beyond relief. Karsner, and also Binger, have shown that prolonged inhalation of oxygen above 70 per cent. is toxic to the alveolar epithelium, causing its desquamation. The result of this desquamation is that the alveolar epithelium fails to function and a cyanosis supervenes which cannot be met by known therapeutic procedures.

A better way is to administer oxygen at a measured rate through a wash-bottle with a good nasal inhaler; other types of nasal inhalers may be employed, such as the Sanford. By this means we have obtained, with a flow rate of four liters per minute, pharyngeal concentrations of 27 to 28 per cent.; in certain conditions, a significant figure. It is necessary to moisten the oxygen or the dry gas will irritate the nasal mucous membranes. (See Fig. 2.)

In small children, and when the inhaler in the nostrils is impracticable because of obstructions in the nose from spurs on the septum, or other deformities, one or two small catheters may be passed into the pharynx through the nostrils. They should be lubricated before insertion, and removed for cleaning daily so as to prevent decubitus in the pharynx. The flow rate should be from 2 to 3 liters per minute. They are fixed to face with adhesive. Patients frequently tolerate them well. At this rate the oxygen in the usual industrial 220 cubic feet cylinder will last more than twenty-four hours.

Unless a flow gauge is utilized, the concentration of oxygen obtained in the pharynx is a matter of guess work. Several varieties of flow gauges are available. To measure the oxygen pressure by the number of bubbles passing through the wash-bottle is extremely inaccurate as it depends upon the temperature of the water and the height of the column through which the gas is passing, as well as the pressure in the cylinder.

In addition to these methods of oxygen administration, by means of which either very high concentrations can be obtained intermittently or moderate concentrations can be obtained continuously, there are the additional devices of tents (Figs. 3 and 4) and chambers, stationary or portable. An oxygen tent which covers all or part of

FIG. 1.



Avoid the funnel method of administering oxygen. It distresses the patient and does not provide a continuous atmosphere of controlled oxygen content. The oxygen cylinder shown is of the old-fashion, low-pressure type, without a gauge to measure contents. It has a high-pressure or regulator in the wash-bottle which a high-pressure or regulator in the wash-bottle greater than the number of bubbles rising the flow rate because the per minute is an inaccurate measure of the flow rate because the height of the column of water with the pressure in the tank are unknown. The flow rate varies with these factors. You do not know how little oxygen may be left in your tank.

FIG. 2.



The nasal inhaler can be used without interruption and will roughly double the partial pressure of oxygen in the alveoli. It must be held in place by adhesive tape, as shown or by a suitable forehead band to hold the high-pressure cylinder and rate of flow. Note also the wash-bottle contents of the cylinder and rate of flow. Dry oxygen irritates the mucous membranes. The ends of the inhaler may be covered with rubber.

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Fig. 5.



What is wrong with this picture?

1. Alcohol flames and matches must not be brought near an oxygen tent.
2. Whenever the canopy is raised, as shown, the oxygen per cent. falls abruptly.
3. No gas analyses or thermometric instruments are in evidence.





the bed, or chamber which permits the attendant to be included consists for the most part of a device for confining the oxygen. When the oxygen is confined and its partial pressure in the tent is raised, there are also confined (1) the water which is evaporated from the lungs and skin, (2) the heat of metabolism of the body, (3) carbon dioxide, (4) certain gases which are eliminated from the lungs and alimentary tract, and (5) the constant beneficial current of circulating air.

On this account, provision must be made for all these factors because if the confiner is not properly ventilated, very high effective temperatures will be reached which are harmful to the patient. When various temperatures are compared, the temperature which is being studied will feel different depending upon the relative humidity or evaporating capacity of the atmosphere and the rate with which it is moved and brought in contact with the surface of the body. Identical temperatures may feel quite different if the air movement and humidity are changed. The standards of reference are the temperature of saturated still air. Studies undertaken by the Bureau of Mines and at Harvard have established a scale of equivalent effective temperatures.

The effect on the pulse and temperature of effective temperature has been studied. At effective temperatures of  $90^{\circ}$  or over with a saturated atmosphere and still air and a dry-bulb temperature of  $90^{\circ}$ , the pulse and temperature rise. If men are working a definite break occurs at  $80^{\circ}$ . Patients with pneumonia, dyspneic, are working hard. Such factors come into play, as seen by the regular rise of temperature of one degree, one-half degrees, or an increased acceleration of the pulse, fifteen beats per minute when patients are removed from the effective temperature of the oxygen chamber. Such a rise in pulse and respiration rate may be sufficient to determine the outcome. Patients should not be removed into less favorable temperatures until they have completely overcome the effects of the oxygen chamber.

The carbon dioxide expired usually reaches a concentration of 1.5 to 2 per cent. Patients at rest breathe comfortably, but become fatigued when the carbon dioxide concentration reaches 2 per cent. Patients with higher metabolism and active circulation become distressed when the concentration reaches 2.5 per cent.

Patients may liberate from 3000 to 4000 calories per day, depending on their fever and restlessness, when they have a temperature; an active nurse may liberate as much. A patient consumes from 300 to 600 cubic centimeters of oxygen a minute and liberates from 250 to 500 cubic centimeters of carbon dioxide. From the lungs there are liberated 600 cubic centimeters of water, and from the skin about 400 cubic centimeters per day.

The effective temperature, which depends on the combined effect of dry-bulb temperature, relative humidity and air movement, should be determined by accurate instruments. For dry-bulb and relative humidity there is required either a sling psychrometer or a dry-bulb thermometer with a hair hygrometer. The rate of air movement can be determined, if the linear speeds are sufficiently great, with an anemometer. If not, a katathermometer or the measurement of the speed of travel of a dust column must be employed.

If measuring instruments are not employed, one may be greatly misled as to the conditions which are being maintained in the tent or chamber and the identical conditions may appear either unpleasantly cool or unpleasantly warm, depending upon the outside atmosphere to which one has become slightly habituated. (See Figs. 3, 4, and 5.) It is probable that there are optimal physical conditions in which to heal various diseases, but concerning these there is practically no accurate knowledge. Certainly, the ability to obtain  $10^{\circ}$  below the outside air, the specification in most air conditioning equipment, may not provide the optimum for disease.

The concentration of the oxygen and the carbon dioxide must also be studied as they are subject to great variation in tents or chambers without one's realizing it unless records are made. We have employed a quasi-continuous oxygen and carbon dioxide recorder which uses the thermoconductivity principle.

We shall now discuss the various devices used in confining oxygen. A consideration of these devices reveals that there are two main types: those which do and those which do not employ blowers or fans for air circulation. In addition to this, they may be grouped by the method employed in attempts to dispose of the factors enumerated as confined with the oxygen. Sometimes two purposes are served by the same device.

(1) Water is disposed of:

- (a) By lowering the temperature of the air so that water is condensed. This is done by passing the air (1) through fragments of ice, (2) over brine coils, or (3) through automobile radiators circulating chilled water, or (4) around vessels containing dry ice or solid carbon dioxide.
- (b) By adsorption of the water on gels of silica, alumina or charcoal with or without the presence of calcium chloride in its pores.
- (2) Heat is removed:
  - (a) By chilling the entire container when possible.
  - (b) By chilling the air (1) which is circulated, or (2) with a cold bunker in tent or chamber.
- (3) Carbon dioxide is removed:
  - (a) It is driven out by the entering oxygen, or diluted by incoming air through leaks or entrances.
  - (b) Soda lime.
  - (c) Sodium hydrate in flakes or as a spray.
  - (d) Diffusion through fabric and solution in water (negligible factors for tents with the gradients involved).
- (4) Odors are removed:
  - (a) By washing the air.
  - (b) By adsorption on gels or activated charcoal.
- (5) Dusts are removed:
  - (a) By air washing, or filters of wire or other mesh.
- (6) Circulation is obtained:
  - (a) By blowers.
  - (b) By convection currents between cold and hot bunkers.
  - (c) By injectors.
  - (d) By bellows.
  - (e) By entering oxygen.

The simplest device, of the type not employing a blower, is an expanded funnel which fits over the patient and may be made either of cellophane or of cotton fabric. Such confiners, when they are made of fabric, are very wasteful of oxygen. If they are made of cellophane, high effective temperatures occur. Where higher effective temperatures are desirable, as in the new-born, this is not a disadvantage. In the case of adults, the effective temperatures become so high that the patients will not tolerate these tents for any

length of time, with the result that the benefits of constant oxygen administration are lost.

Another type of tent, without a fan or blower, depends for its circulation upon the air injector which is attached to the high pressure oxygen cylinder. The air injector is set for about five or seven liters of gas per minute, and is almost independent of the pressure in the cylinder except that it requires a minimum pressure in the tank for operation. With it, if the tent is relatively leak-proof, high concentrations will develop so that if such a tent is placed over a small child who does not displace the tent, concentrations of 70 per cent. or more may be achieved. With adults and with restless patients, dangerous concentrations are not achieved. The disadvantage of the higher concentrations may, however, be overcome by the insertion of an artificial leak or escape.

The first tent of the other type, utilizing a fan or blower, was built by Roth and Barach. This depends on the circulation of air through ducts and the passage of the air over cracked ice. In this tent, as originally designed, the ducts are so small that the circulation is not always adequate to remove the heat from the patient. As a result the tent may become heated and the patient refuse to remain in it unless the surrounding atmosphere is also chilled. The device of having the escape of oxygen or the cooled air near the face of the patient adds to the comfort of the patient but does not militate against the very definite disadvantage of otherwise insufficient circulation.

The problems of chambers, whether stationary or portable, is like that of tents in respect to the conditions which must be met. The details are subject to the restrictions of material and dimensions, and it must be borne in mind that as the size of the chamber increases the surface is relatively less large.

In our special chamber at the Harlem Hospital, which is a steel, rubber-gasketed room, insulated, the air is circulated through an automobile radiator through which the tap water runs. With this we can obtain temperatures to within 2 or 3° Fahrenheit of the water employed for cooling when the water is 62° to 64° Fahrenheit. Under ordinary conditions this is quite satisfactory. In the late Summer and Fall, when the water of the reservoirs is heated to 72° or 73° it is less useful, and other methods of cooling must be instituted.

The water liberated by the lungs of inmates, patients, and nurses amounts to eight or ten pounds a day but provision should be made for removal of much larger amounts of water because water-laden air is admitted to the chamber on entering or leaving it, and in the Summer or on humid days as much as eighteen pounds may have to be removed by the gcls. Concentrations of carbon dioxide reaching 3 per cent. may occur, and on this account it is necessary to remove the carbon dioxide. In our chamber at Harlem Hospital we remove the carbon dioxide by passing a portion of the air over a tower of sodium hydrate flakes, and the carbon dioxide can be removed at a cost of one dollar a day. For the same amount of decarbonation, employing soda lime, the cost would be about seven dollars.

In our chamber at Harlem Hospital, the air is filtered by passing over wire mesh covered with glycerin, and the odors are removed by passing through beds of silica gel. The air in the chamber is changed once in three minutes, and in that length of time odors are usually removed.

Tents are not as economical to operate as chambers, considering the number of patients treated. A chamber accommodating two patients and a nurse, with fifty entries a day, can be operated at a cost of nine liters of oxygen per minute. A tent for one patient may require as much as eight or ten liters.

When one realizes what must be accomplished in order to maintain good conditions in a confined atmosphere, it is possible to design tents and chambers with intelligence. Many of the tents in use have been designed without adequate consideration of these requirements.

A great deal of the efficiency of a tent or chamber depends upon the training of the operating personnel. A tent should never be removed for the treatment of the patient because by this means temporary anoxemia may supervene. The food should be handed to the patient by sliding it beneath the tent, and when the patient is bathed the tent should be draped about the patient's neck. The advantages of our own tent, in which the air is blown through a radiator, are that there is no loss of oxygen when the ice is changed. It is probable that very little carbon dioxide is removed by solution in water as we have found that the carbon dioxide concentrations may rise, in spite of the passage of air over ice, to 1.5 or 2 per cent. in

tents ventilated by blowers, and to as much as 2.5 per cent. in a tent without a blower, ventilated by an oxygen injector.

Great care to prevent conflagrations must be exercised when operating tents or chambers. Oxygen under pressure and oil form an explosive mixture. Gauges should not contain oil, or be oiled. The fires which have occurred in connection with the employment of oxygen have been due to carelessness in the presence of oxygen when combustion is accelerated. Patients in tents and chambers should be searched for matches and smoking utensils. No electric sparks should be permitted near oxygen-enriched atmospheres. Chambers should not be so long that static may develop by the movement of persons in the chamber. The walls of metal chambers should be grounded. Pails of sand, or an adequate supply of running water which can be readily released, should be available. The attendants should at once stop draughts and oxygen flow, in the event of a conflagration, and should open doors to release the oxygen. (Fig. 5.)

The careless transfer of tents or oxygen apparatus from patient to patient may be responsible for cross infections, especially if streptococci are involved. On this account, the Committee on Public Health Relations of the New York Academy of Medicine has recommended the following method of disinfection:

"All tents should be sterilized after each use by scrubbing inside as well as outside with soap and water. This work could be facilitated and made more effective if the tents were made of double-faced material. After scrubbing, the tent should be dipped in a solution of 1 to 10,000 of bichlorid of mercury for five minutes. To prevent incrustation, the tent should be washed down with water after immersion in the bichlorid of mercury. In hospital practice, an alternate method would be the dipping of the tent in a 70 per cent. solution of ethyl alcohol. An inexpensive method of sterilization is to expose the tent for forty-five minutes to formaldehyde vapor followed by fifteen minutes' exposure to ammonia vapor."

#### SUMMARY


According to the classification of Barcroft, amplified by Peters, and Van Slyke, four types of oxygen want in the body are recognized: anoxic anoxia (decreased per cent. oxygen saturation of the arterial blood); anemic anoxia (low oxygen saturation capacity of

the blood); stagnant anoxia (slow transfer of oxygen due to decreased circulation); and histotoxic anoxia (inadequate absorption of oxygen through the tissues). The last three types do not respond appreciably to oxygen therapy.


Anoxic anoxia, or true anoxemia, varies in intensity and symptoms according to the decrease in per cent. saturation of the arterial blood. When the state of unsaturation is present as the blood leaves the lungs, it may be completely or partially relieved—unless there

FIG. 6.

## GIVE OXYGEN EARLY

Lavanzin  did without food  
forty days

A camel  can do without  
water a week

 We can live without water  
three days  
Complete oxygen deprivation is fatal  
in nine minutes

Release the strangle hold  
Meet the early call for oxygen  
It is an emergency—be prompt  
Don't wait until your patient is moribund!  
Give him a fighting chance against infection  
Don't save oxygen and lose your patient!

has been a shunt from venous to arterial blood through capillaries not accessible to air—by increasing the partial pressure of oxygen in the alveolar air to an extent that should be adjusted according to the degree of unsaturation present. If the alveolar oxygen concentration is increased uniformly from 16 per cent. to 60 per cent. or more, the degree of saturation of the blood will rise at first rapidly (as a dry sponge soaks up water), and then more and more slowly as it approaches 96 to 100 per cent. of its full oxygen capacity. From then on it remains almost unaffected by increase in oxygen tension. In some cases of anoxic anoxia, the low per cent. saturation of the arterial blood is caused by a shunt of venous into arterial blood after the latter has been normally saturated. In these cases, the condition

will be little if at all benefited by inhaling atmospheres rich in oxygen.

Dyspnea, lack of mental coördination, and increase in pulse and respiratory rates should be recognized as early symptoms of anoxia. Cyanosis is not always present, especially in cases of anemia, and should not be used as the criterion for initiating oxygen therapy.

FIG. 7.

## WHAT IS A TENT?

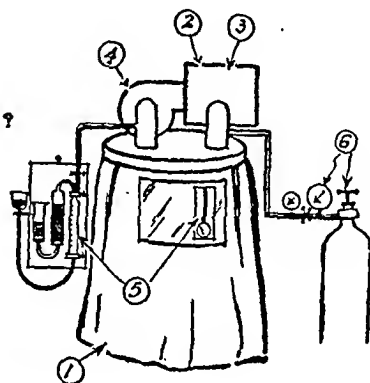
R

MISCE

et

FIAT

1. Oxygen Confiner
2. A Cooler
3. A Moisture-Remover
4. A Circulating System with Ducts
5. Analytical and Meteorological Instruments
6. Oxygen tank and gauge



A GOOD TENT when it maintains suitable  
effective temperatures and proper oxygen  
concentration without waste and with  
little noise.

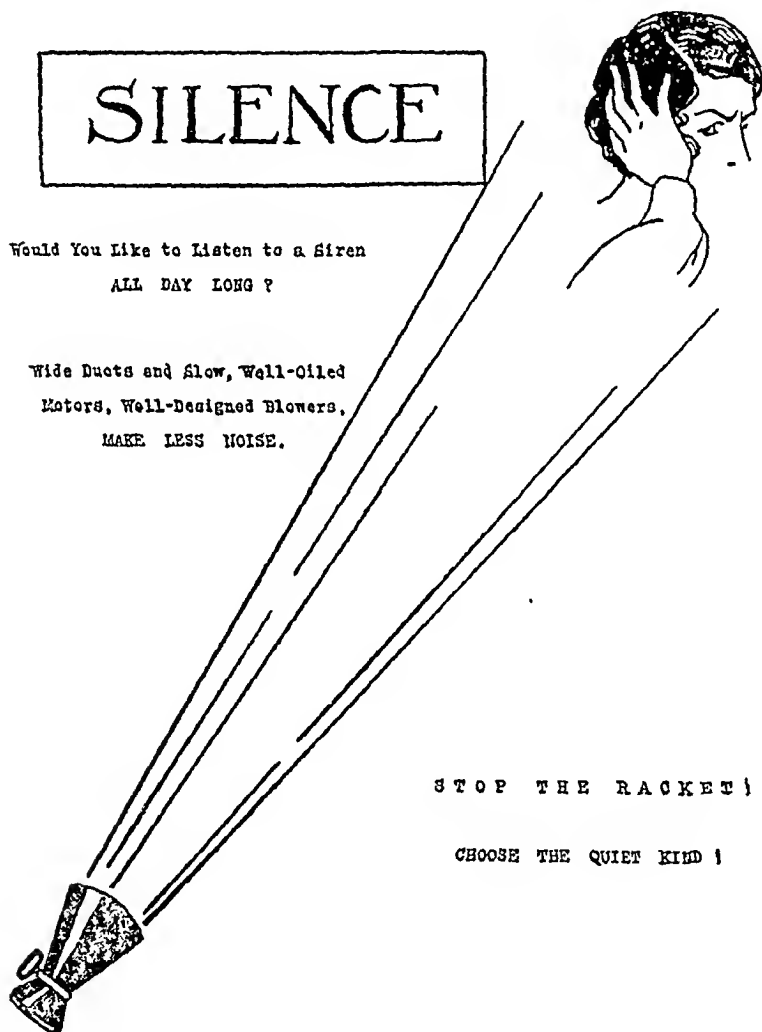
Oxygen should be given promptly and continuously in the earliest stages of oxygen want. If the symptoms are not alleviated by inhalations of as much as 50 to 60 per cent. oxygen, the condition is probably due to complete stoppage of circulation through a very large capillary bed.

Six methods of administration of oxygen by inhalation are discussed. The mask and funnel methods are considered to be the least efficient. They both require constant supervision, are dis-



trussing to the patient, and do not lend themselves to proper control of the concentration of oxygen. Nasal tubes—catheter and inhaler—are adequate for mild anoxias if properly adjusted, and have the advantage of simplicity and cheapness.

FIG. 8.



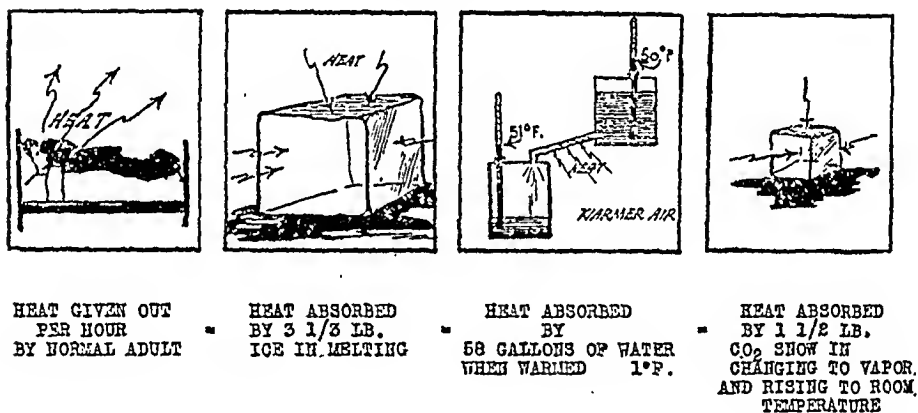
Oxygen chambers and tents are most satisfactory for oxygen therapy. If well designed and properly operated they permit adjustment of the concentrations of oxygen and carbon dioxide according to individual needs, as well as control of the thermal environment—

dry-bulb temperature, humidity and air movement—so as to facilitate heat loss from the body. The latter factor is of great importance in cases of oxygen want, since heat loss is regulated by circulatory control, and therefore an environment unfavorable for heat dissipation provides added work for an already overburdened heart.

The technic of atmosphere control for tents and chambers is

FIG. 9.  
COOLING REQUIREMENTS  
for  
OXYGEN TENTS

EQUALS



ADULT WITH TEMPERATURE OF 105° F.

GIVES OUT

50% MORE HEAT THAN NORMAL ADULT.

UNLESS THIS HEAT IS CONTINUOUSLY REMOVED  
HE WILL SUFFER HEAT EXHAUSTION.

discussed with reference to the special instruments required. The need for special nursing procedures is emphasized, as well as the need for guarding against fires and explosions and against the danger of cross infection from unsterilized equipment.

In February, 1931, an exhibition of oxygen therapy apparatus was held under the auspices of the Public Health Relations Committee of the New York Academy of Medicine. One of the exhibits,

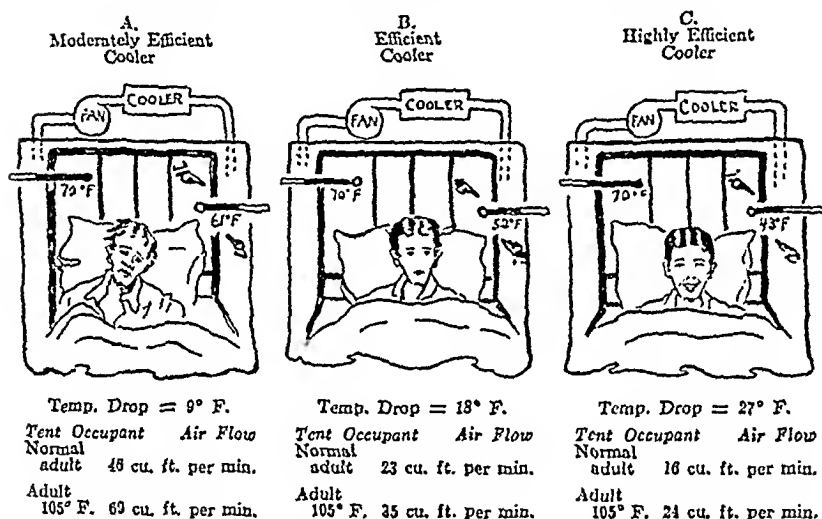
prepared by the Littaner Pneumonia Research Fund of New York University, consisted of a stereomotorgraph showing of slides illustrative of the principles underlying the construction and operation of tents. This was termed "A Primer of Oxygen Therapy," which is

FIG. 10.

# HOW FAST SHOULD THE AIR IN YOUR TENT BE CIRCULATED? REMEMBER THAT

*A Small Volume of Air, Cooled Many Degrees  
has removed as much heat as  
A Larger Volume, Less Efficiently Cooled*

## ESTIMATES FOR A TENT AT ROOM TEMPERATURE



STILL GREATER COOLING CAPACITY IS NEEDED  
TO KEEP TENT TEMPERATURE  
LOWER THAN TEMPERATURE OF OUTER ROOM  
TEST THE COOLING EFFICIENCY  
AND THE FLOW RATE OF YOUR TENT

(See Chart)

herewith presented in part as it is intended to instruct physicians in the operation of tents and in the selection of what is desirable in design. My thanks are due to P. Dodd Ackerman, Edith T. Woolf, and Chas. L. Pinci for their valuable assistance in the preparation of the posters (Figs. 6-10) and lantern slides above mentioned.

# Anthropology

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## THE ORIGIN OF MAN

By PROFESSOR HANS FRIEDENTHAL

Berlin, Germany

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DARWIN published his "Origin of Species" in November, 1859, and his "Descent of Man," in February, 1871. During this period, and until the time of his death in April, 1882, Darwin ably defended his viewpoints, and successfully confuted all his critics, and today his explanation as to the origin of man is more firmly established than ever before. This latter statement is made with the full knowledge of many statements to the contrary and of the large amount of experimental and research work done to disprove his theories or at least to show that they are still unproved.

In this connection, it is worthy of remark that the very ones who thought that their writings and investigations had made Darwin's theories untenable by advancing the principle that all animals, including the apes, were descendants of man, have presented the strongest kind of experimental evidence to show that Darwin was right, by bringing forth facts which were not available to him during his lifetime. This remark applies especially to embryologic investigations and to the biogenetic fundamental law of Haeckel, whose views, however, are often misquoted, for he does not merely say that the first half of embryonic life only repeats the past, but when correctly stated Haeckel taught that while the first half shows a predomination of repetitions of past life there are also present signs of progressive developments, and that while the latter half of life reveals an excess of developmental progress, it also exhibits degressive signs as well as in the first portion of life. This statement of Haeckel's is especially applicable to the developmental period of man, and the writer would stress that no one living animal species should be considered as having originated from any other living animal species, but that both of them originated from a common hereditary stock of the past.

The tendency to follow the simplest trend of reasoning in thinking of all animal species as having originated from one forefather seems hard to eradicate. One must remember that, just as each single individual, so each type of animal had, not one forefather, but must have had an indefinite, and in some instances, an incomprehensibly large number of forefathers. A deception in reasoning occurs where it seems as though one individual were the forefather of innumerable generations, for less than two ancestors are inconceivable for sexual progeny. One forgets that with the word forefather man has set an arbitrary starting point which could not have existed in nature.

According to modern conceptions, held by the author, mankind did not spring from any species of apes now living, for instance from the chimpanzee, as many present zoölogists are inclined to believe, but man and chimpanzee have a common origin in animal species which show partial relationship to quite a number of other living apes.

By the results of modern precepts of heredity, which have disclosed entirely new vistas in the natural sciences, the author believes that he has shown the nature of the unique position held by mankind in the zoölogic system. He has demonstrated why mutation of species of organisms was necessary and possible in the past, while the development of man, in contradistinction to all animal types, seems not only possible but necessary in the future. This may be deduced from the conditions, at present recognizable as placing mankind in its unique position. For his genetic position, his variability depends on the possibility of fertile crossing of living species with different, or similar hereditary stock. In the language of genetics one would say that variability of species depends upon pure or split heredity. The unique position of man in the present animal series rests with the fact that he originated in split heredity from a succession of anatomically different forms, which are fertile in unlimited crossings from which necessarily ever new forms of man arose. The reverse, that is, pure heredity, scientifically termed homozygosis, is characteristic for the animal and vegetable kingdom. In many instances it has gone on for millions of years, and, lacking neighboring forms, made rejuvenation by hybridization with closely related hereditary material, which would make the starting of new animal types impossible. When the science of heredity speaks of pure hereditary lines it thereby indicates that no change can be ex-

pected from pure hereditary strain, and that the respective forms are restricted for all future to their especial type; it could be changed only by bastardization of hereditary material with new characteristics. This conception explains the applicability of the law for the animal kingdom according to which an evolutionary tendency, once begun, cannot be changed. This idea is correct for pure hereditary strains, where hybridization no longer enters into the problem, because all closely related organisms have died out. This statement is wrong as long as relatives of this animal type still exist by which a change or reversal would be possible by adding new hereditary units in bastardization.

Even if developmental impetus of oval cells of the anthropoid apes by human semen were possible by artificial fertilization, which, according to the author's blood studies, is very probable, hybridization of man with non-human hereditary stock cannot be considered. Nevertheless, an expansion of the variations of human type formation by adding new hereditary units from apes is out of the question. It is true the author's blood studies demonstrated that man and anthropoid apes react, both in precipitation and hemolysin tests, like animals among which fertile crossing is possible. Man's blood is as closely related to that of the great anthropoids as is the blood of horses to that of asses, or that of hares to that of rabbits, or the blood of foxes to that of dogs. The greater anatomic difference existing between man and anthropoid apes as compared with that existing between the animal types mentioned, cannot be denied. This is especially evident in the mature male. The surprising similarity, however, of the juvenile forms of man and of the anthropoid apes points to the relatively brief period which has elapsed since hominides and anthropoids separated. The surprisingly fortunate findings of man-like apes, and anthropoid-like human forms of the past make it seem certain that types existed at the close of the Tertiary period which Darwin in his day called the "missing link," conjecturing that they formed the transitional forms between man and ape. Weinert, in his "Men of the Past" (Enke, Stuttgart), writes that it was by an inconceivably fortunate chance that the Dutch scientist, Eugen Dubois, who set out in quest of this missing link predicted by Darwin, actually found it in the remains of *Pithecanthropus* in a region where no one before, or after, has succeeded in discovering transitional types. If

similar remains have been found to-day near Peking it proves the distribution of such types over a restricted area of this world, but not the marvelous fortunate coincidence of circumstances which lead Dubois to the spot whence, according to his opinion, which need not be correct, mankind spread over the earth.

If controversy continues today, regarding the identity of *Pithecanthropus* as the actual forefather of present-day mankind, it would point to the above discussion of the impossibility of a single forefather. Nothing, however, could characterize the nature of the find better as the link between man and ape, than such controversy of the best informed men, on whether *Pithecanthropus* has more human or more ape-man traits. The discussion centers about the question as to whether, as would be the case with an assumed bastard between man and anthropoid ape, *Pithecanthropus* should be considered as an intermediary link between man and to-day's apes. The impression of predominantly human, or predominantly ape-like type, varies according to the tastes of the investigators..

The author believes that other animal forms existed in the times of *Pithecanthropus* which were physically so closely related to him that crossing was possible, and that mankind of to-day unites within it not only the blood of *Pithecanthropus* but also that of other closely related animal species, living at that time.

A crude statement of the deductions sounds strange, namely, that man is the most "bastardized" living being on our planet and therefore the type most capable of development. In our domestic animals, we see the reasons which suggest that it is actually the mixture of non-identical hereditary material which is the cause of modifications of organisms and, possibly, it is the most important of all guiding principles for future investigation.

If genetics to-day place great value on accidental mutations, even in so-called pure strains, the author points out that such mutations need signify nothing but remainders and reminders of former split-heredity. A perfectly pure strain would not produce mutations. The farther the hereditary material is from the pure strain, however, the oftener does mutation occur, until ultimately panmixia results. We see it on earth in domesticated animals and man, where each individual represents a form which has never existed in exactly the same shape, and which will never occur again in identically the same form.

This is different from the rigid types of the pure lines which we see in the majority of animal and plant types living to-day.

The characteristics of domestication in man are really wild animal characteristics. But if one defines those animals as domestic, the free propagation of which is curtailed, and whose breeding is regulated by man, all animal types which man breeds and approximates to himself will develop signs of domestication by hybridization of similar types, which, once produced, are not bred over into purer hereditary lines by their split-heredity resulting from selection by man as are wild animals in natural selection. Just, as everywhere in nature, hybridization occurs first, among our systematically bred domestic animals, then comes breeding of races. In bringing together animal types which would never have interbred in the wild state, man reestablishes the former split-heredity, and, with it, variability of types which was lost in the pure strains. Therefore, marked changes are now not to be expected without intervention of man.

With rare exceptions no deliberate racial breeding has been attempted among mankind, but there exists a certain irrational, panmixture of all existing human forms. In a few instances reduction of choice of partners was the aim in caste formation to which one, however, never strictly adhered. In a zoölogic sense, nobility and royalty are not of pure lines, but rather of split-heredity, as are most men living to-day. Systematic race formation among mankind will be possible only when eugenic laws are not only formulated, but acted upon. In this sense, apostles of the Nordic race, within reasonable limits, are advocates of systematic breeding of the most rational and perfect of human types. There is no scientific importance in choosing to call them Nordic, but the systematic selection, and the restriction of unsystematized intermixture will probably appeal to most scientists.

We must assume that hominidae back into the unknown past were adaptable to every climate on account of their mixed inheritance while animal species of pure lines became restricted to ever smaller climatic areas. We may assume that early, even in diluvial times, Neanderthal men migrated, and populated any accessible portion of earth's surface by hybridizing all human beings physically related to them. Intermixture, then, is no recent sign of degeneration of mankind which has given occasion for pessimistic predictions for the



future of mankind. The reverse is the case, for it is the very reason why man alone, of all animal types, has remained so young with his ever renewed split-heredity, which most other living beings have forfeited.

All the features of domestication which man shares with his true domestic animals, appear comprehensible in the light of genetics which teach artificial production of such features in other animals. In this sense one might consider drossphylla, the preferred animal for experimental genetics of the zoölogists, a domesticated animal, for its variability, artificially produced by man, is its main feature of domestication, not taming, or training, for man's purposes. If he so desired, man could easily produce human types with six fingers, or with tails, or with hair resembling that of dogs, if there were any sense in it. But so far no eugenist considers reason the primary of all the qualities which make man man, and its propagation the first eugenic requirement for man. Future man should be good, wise, healthy, beautiful, valuing these qualities in the sequence named.

In strict delineation of the word race and those individuals who show hereditary features of a different race, to be logical would have to be considered the genuses of the same animal form and as belonging to a different race. Since the botanist calls two peas from the same pod, which he has produced by auto-fertilization siblings, if one of the peas produces pink blooming, the other white blooming descendants, how much more would we have to consider man and wife as of different races, more especially since one can now prove the differences of chromosomes in man and woman by photography. Anything that is said about differences of racial mentality, and differences of physical and mental qualities among the various human races, is simplest understood when one remembers the differences presented by man and woman of the same species.

Unfortunately, science has not yet adopted a uniform use of the word race. It is used strictly logically by the botanist, but there is great laxity of application in common usage of calling men with light skin the white race irrespective of all other hereditary differences. The author finds the application of the names of to-day's animals to remains of other animal forms found in the soil, just as incorrect, for instance, calling Taunge ape found in Betchuana a chimpanzee in spite of all the differences. The features distinguishing those former

creatures and the chimpanzee may have been manifold considering those found in the scant remains. We know neither his pelvis, nor the conformation of his foot, nor his hair or length of arms, or mode of living, or development, so that the classification must be supplied with ample question marks. The author surmises that the characteristics of specimens of this type still to be discovered will not all be chimpanzee-like, but that some will be shared with man, others with orang, gorilla, hylobates, and other apes. Such remains are classified with those already known from an urge for logical systematization, neglecting the former split-heredity which may have caused approximation to entire groups of different animal species in the reconstruction. We will touch but briefly upon the main distinguishing features which seem to divide the hominidae and the anthropoidae by a deep chasm, especially when they are described in the above ill-defined manner, as is unfortunately too often the case. Even now zoölogists and evolutionists describe the lack of hair in man as a feature supposingly separating him from all other animals, while, in reality, a great number of the lower mammals are far more lacking in hair than are many of the human races. There are, for instance, mammals, such as the Narwal, where no trace of hair can be discovered. There are naked moles, naked bats, which have much less hair than the human types.

If one, however, wants to show the relation of man to anthropoids, present hairy covering of man affords an interesting subject, and will be discussed in detail later on. The author found the only actually fundamental difference of man's hairy covering from that of all other mammals in that man has not a single blood-sac or sinus hair, while all of the other hair-bearing mammals, without exception first develop the blood-sac hairs. About the mouth of the orang we find all transitional forms between the blood-sac and plain hair, which shows that in this ape the blood-sac hairs are beginning to disappear. There is as yet no proof that man formerly had blood-sac hairs, yet there is an interesting proof of probability. Bromann and other investigators found in a projection on the ulnar side of the arm of human embryos in a stage where the hands were still like fins, such as is found in the embryos of wild animals and which later are covered with stiff tactile bristles. The conjecture is that they serve animals who run through narrow passages for exact orientation. Beginnings

of such organs have been demonstrated in several human embryos although beginnings of blood-sac hairs were absent.

Further the author found intra-uterine development of a long hair cap in anthropoid and in some lower apes, such as is seen in human embryos, although only the adult human develops a long hairy mane. Distinctly light colored soles were found in fetuses of chimpanzees which become dark black in the adult animal. In this ape embryos resemble Negroes whose light soles form a marked contrast with the dark color of the rest of their body surface.

One of the most distinctive features of man, the human foot, has attracted the attention of scientists for a long time. The erect gait must have influenced its formation. Here also, transitions lead everywhere from human features to all animals, therefore the human foot is not anything principally new in an anatomic respect. The author rejects the construing of zoölogic differences from use or non-use. Even to-day man has a prehensile foot like anthropoid apes, and he can develop it to a considerable degree of functional perfection by practice, as there are all the necessary muscles for grasping. On the other hand it is irrelevant as an argument, if most men after birth change their feet by shoes, other maiming measures, and constant walking on the ground to a running tool, incapable of prehension. The fact which Büllz reported, that Japanese women even now can pinch with their toes may be explained by their not wearing shoes. When Australians wished to appear unarmed they took their spears with them, carrying them with their feet. A number of human infants in my Infants' Home held their milk bottles with both feet so they might play with their hands while drinking. The same applies to the non-existence of a prehensile foot in hominidae and the lack of hairy covering of man. Such differentiations from apes do not exist. They are the result of the desire to erect insurmountable chasms between man and the neighboring animal types.

Professor Westenhöfer uses the fact that accessory glands are found more often in man than in the rest of the apes, to prove former aquatic habits of man's ancestors. He points to the plurality of spleen of many of the aquatic species as compared with the single spleen in apes and man. That the long legs of man, as compared to the short legs of many ape species remind us of long-legged wading birds which find their food in shallow waters, cannot be denied.

Even to-day the children of Teneriffe find their food by wading in the ocean, searching for food with their feet, but grasping it with their hands, to devour it raw. This type of feeding which never is seen in apes would, it is true, lead to an advantage of the long-legged individuals over the short-legged, and a natural selection might lead to an increased average of long-legged persons. The author, however, does not believe that such a beach life should be considered the only reason, or even sufficient explanation for the relatively long legs of man, for which a great number of already known correlations exist. We know that long persistence of cartilage at the osseous borderline of the extremities suffices to increase growth of the extremities. Therefore, the length of limbs is dependent upon the greatly varying period of maturation of the individual, for generally all growth ceases upon full maturity of the endocrine glands. Delayed maturity causes lengthening of the extremities. Striking are the long extremities of eunuchs from whom the restricting generative glands have been removed. The long extremities of oxen as compared to those of bulls are well known.

Even a weakening of the generative glands, as is common among degenerated city dwellers causes increase of individuals with excessively long extremities while healthy specimens of the rural population have shorter limbs. The behavior of the endocrine glands, however, is not the only factor in determining the length of the extremities.

Professor Bolck has repeatedly pointed out the persistence of embryonal characteristics in man, although he did not surmise that such persistence might be due to continuous hybridization, which meant rejuvenation of the species. The unique position of man becomes evident only when the sum of variations is taken into consideration. Upon diligent search each single differentiating feature can be found in other organisms, even where they are not expected.

Man is distinguished from the majority of mammals by the weight of his brain, as compared with the rest of his body and yet there are mammals, among them apes, which have relatively much heavier brains than man. Bolck stated that man is the only land-dwelling mammal copulating in a breast to breast position but eye-witnesses report the same posture among Orang Utang, beaver, and porcupine. When in the upright position the sexual organs and the

anus of the female are not visible, as they are in all other mammals, while in chimpanzee these organs seem to be placed far back. The orang, the only animal among the Old World apes, with a forehead, has a number of features which make him closer related to man than to all other animals, including the chimpanzee, and the precipitin blood reaction is so marked as to confirm this relation. This does not exclude the greater divergence of a number of orang characters from man's than is evident in chimpanzee whose likeness to the European human type is especially pronounced, while southern Asiatics have an instinct for their especial resemblance to the orang. The prominent frontal sinus in the chimpanzee is dependent upon the slight bulge of the frontal portion of the brain of this ape, while the steep forehead of orang who has no frontal sinus, corresponds to the weakly developed frontal sinus of the Asiatics, whose forehead is steeper than that of the original European type, or present types resembling it. Conditions prevailing in domestic dogs show that too great importance should not be attached to the existence of a frontal sinus, where the difference of skulls among dwarfs and giant types is almost as pronounced as the difference in skull conformation of man and gorilla. According to Professor Viktor Mayer, the smallest dog species have no frontal sinuses, or only atrophied remnants of such, while the large species have two large frontal sinuses, and the medium-sized often but one.

The balloon shape of the head which is common to all fetuses of mammals hinders the development of a frontal sinus, irrespective of the animal species. This coincides with the dwarf dogs and the dwarf hippopotami which do not develop frontal sinuses when living wild, while the large hippopotami have very pronounced frontal sinuses.

The elephant holds a unique position. Its Indian representative has a wall of frontal sinuses across his entire skull. It serves to break down trees which hinder his progress. The African elephant has much smaller frontal sinuses, therefore a flat, receding forehead. Orang Utang has no frontal sinus, and yet presents a large negroid forehead resembling that of the human, while the high forehead of the Indian elephant creates the impression of being high because of the powerful air chambers, yet the brain does not differ materially from that of the African elephant.

Before taking up more in detail the classification of man the author would like to point out briefly to the interesting conditions existing between the human and the anthropoid races of the same locality. The teachings of heredity deny that these human and anthropoid races of the same regions are closer related to the anthropoids of these regions than are other human beings. Comparing the diameter of the hair of negro and gorilla, of the white man and the orang we find a startling similarity between negro and gorilla, and between the orang and the white man. Taking temperaments of the animals into account we may even detect three subdivisions. The quiet, apparently phlegmatic ways of the orang who create a melancholic impression, similar to that of many Asiatic races, while the chimpanzee, ever lively, aggressive, and loving motion shows resemblance to the temperament of southern white races and the greater part of the black race, which may well be likened to that of the gorilla. The movements of gorilla and chimpanzee, especially their dances when living wild resemble those of the Negro and the southern Europeans, but not those of the Asiatic races. Negroes, gorilla, and chimpanzee have the drumming with hands and feet, and the beating on resounding objects in common. The relation of the sexes among the different anthropoid apes is still unexplained. The author believes that chimpanzees do not form family groups but that, as among dogs and cattle, where they live in herds, there is a relation of sexes resembling maternal human society rights rather than the paternal. This is evidenced anatomically in the appearance of the male, for only gorilla and orang have visible combative weapons while male and female chimpanzees show little difference, just as in dogs, where no battles are fought for the female, but where, as among mankind of the past, matriarchal conditions gave the choice of partner to the female. As there are, however, chimpanzees who do not live in large hordes there may be individual aggregations with beginning paternalistic rights.

Wherever there are marked differences in the male among the ape series we find polygamy and despotism while juster conditions prevail where male and female are similar. In the same sense one notices fairer social relations between the sexes among human beings where the outward sex characteristics are less marked, or artificially reduced, or promoted by custom and law.

## THE CLASSIFICATION OF MAN IN THE ANIMAL KINGDOM\*

That a really satisfactory classification of man as a member of the zoölogic system presents great difficulties and has not been forthcoming, will readily be appreciated by the intelligent reader from the views expressed in the first portion of this paper, so it is not astonishing that agreement even among zoölogists themselves has not yet been reached regarding the nature and the extent of the separation of mankind from the nearest related ape species. The reason for such difficulties lies not only in the firmly established meaning of the word man which gives to him in many respects a separate place, is constantly interrupting a purely zoölogic aspect by accustomed mental bridging. Furthermore animals are the easier classified in a system the older the species is. Difficulties similar to those encountered with man apply, though in a lesser degree, to the latest animal species, especially when the domesticated animals are under consideration for classification.

In the newest zoölogic textbook only a modest suborder within the order of primates, is apportioned to man, while formerly man was placed entirely separate from the entire animal kingdom. In an illogic manner zoölogists use the words ape and man as contrasts though they classify them in the same animal order. Everywhere in zoölogic literature characters of man are called apish, while, actually, each human characteristic must be an ape characteristic, if man is placed in the order of apes.

The author believes that a solution of the systematic difficulties, satisfactory to all, can be found only if the present forms of man and other primates alone are taken into consideration but also serologic blood relation and the remains of former transitional links found in the soil. Unfortunately we constantly meet with the tendency in zoölogy of deriving one animal species from another, thereby representing one as original form of another animal species living to-day.

The author has repeatedly pointed out that it is just as impossible for man to have descended from one forefather as it is for mankind to have descended from one animal species. If, therefore, discussion arises about monogenetic and polygenetic origin of an animal type,

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\* Based on remarks made at Berlin, Germany, before the Society of Mammalogy on April 13, 1931, and especially prepared by the author for publication in the INTERNATIONAL CLINICS.

the polygenetics must always be right, as less than two original parents are out of the question for sexually produced individuals. For the past we must accept animal species which do not correspond to our present system, as they represent connecting links between the present manifold forms of life. Even if we may speak of every present-day ape, under certain circumstances, as belonging to the chimpanzees, or not, we will—providing Darwin is right, and evolutionary theories are justified—find remains of forms in the soil which, with all their characters resembling chimpanzee, will show features such as are at present found in man, orang-utang, gorilla, and in many neighboring forms of the chimpanzee. How numerous such discoveries are, is well known, also how we have succeeded in finding preliminary forms of mankind, which, aside from parts known as purely human, have traits which are known to-day only in other living apes. The words missing link do not sound good to a careful scientist for every systematician endeavors to take over, as far as possible, the present latest classified groups, that is the species, to apply them to the classification of the past. Not all zoölogists recognize that such endeavor has its limitations and that it leads to erroneous results, if actually all organisms of the hereditary material of the past are connected.

If a separate subspecies is apportioned to the hominidae in the present zoölogic system, it would signify that man and the anthropoid apes differ in the same manner as do the anthropoid apes from the present monkeys. This expresses distinctly the incorrectness of such classification. If we apply the author's results of blood studies to the zoölogic system of hominidae the result is, that man and the other anthropoid apes in their blood serology, act like animals of *one animal family*, which may sometimes produce living bastards upon hybridization. According to blood studies success of fertilization of the ovum of anthropoid ape females with human sperma is very likely, for the blood of man differs no more from that of the anthropoid apes than the blood of rabbits from that of hares, or the blood of asses from that of horses or of dogs from foxes. It is known that crossing of horse and ass produces a new animal form, the mule, the males of which have proven infertile so far, while it has been possible, repeatedly, to produce living offspring upon crossing mule females with one of the original species. Though the production of living bastards of hare and rabbit has not been entirely proven, no systematician



would attempt to place these animals in two different families. When one injects orang blood into the rabbit the serum, mixed with human blood often shows stronger reaction than when mixed with the blood of other anthropoid ape species, sometimes even stronger than when mixed with other individuals of orang. Under these circumstances exact determination of very closely related animal forms is unlikely to succeed unless methods of investigation become more refined than they are at present. The necessity of placing hominidae and anthropoidae in one zoölogic family is established. The newest findings derived from the earth's crust agree with the serologic findings, for animal forms have been brought to light which it is difficult to class either with hominidae, or not to do so. Darwin spoke of a missing link, a transitional link between man and ape, which he believed must have lived if his theories were correct, and, as is well known, the ape-man conjectured by Darwin, an intermediate form between man and to-day's anthropoid apes was found. The Dutch physician Eugen Dubois set out to find this link, and found it in the remains of *Pithecanthropus* of Java. Recently more numerous remains of *Pithecanthropus*-like pre-human beings have been found near Peking. It is difficult to substantiate the classification of *Pithecanthropus*, the true ape-man, either with man or one of the present-day anthropoid apes. As theory would have it, the remains of pre-human forms show relations to a number of present living beings, but not to an individual animal species. According to the author's opinion the belief of having discovered the forefather of mankind in *Pithecanthropus* would be erroneous, for there could not have been a single forefather, but a series of preliminary forms, from the mixture of which present ape species and ape families, and among them man, have originated. It will be hard for zoölogic systematicians to relinquish the convenient single hereditary theory and to become accustomed to the thought that a different genetic situation prevailed in past species formation than applies to most of the present organisms, excepting the domestic animals. The theory of descent of man, if we would correlate it with modern conceptions, demands that we consider organisms, capable of development in the past, as of split heredity, the present as of pure lines. If an organism has become pure strained all possibility of development in certain directions ceases, and loss mutation alone produces changes, while new qualities

can no longer be produced. If, however, there are similar, but not identical, organisms near which are capable of fertile mating, such cross-breeding may produce rejuvenation, and afford a stimulus for formation of new species. This is impossible if neighboring forms no longer exist, to mix with the original form. The genetic condition of a species as that of an individual lies in the possibility of meeting on the one hand identical hereditary stock, or such that is similar, but after all of different hereditary stock, on the other hand. If identical partners only are available, development is closed; if there is a possibility of introducing new hereditary factors, developmental faculties are theoretically without limit.

Dollo's law, which states that a certain developmental direction, once incited in organisms, can never be reversed, this applies to pure strains only. According to present genetics one cannot see why developmental directions, once assumed, could not be reversed if crossing introduces new hereditary factors. Only if all animal forms had grown into pure strains would Dollo's law have full value. At the moment when there will be no other species on earth, with which to interbreed, none but "loss" mutation can be expected in an animal species and more pure strains must result where inbreeding is increased. In this sense every isolation of organisms tends to ever purer strains while every mixture leads back to the formerly customary split heredity. Every restriction in the choice of sexual partners leads to increase of pure strains, every sexual urge, however, may lead to expansion of hereditary possibilities of the species, providing genetic conditions permit.

One of the chasms existing in our feelings between animal and man, at least for the Nordic, is the scant hair covering of mankind, generally termed nakedness, although there are many mammals which have much less hair than man. As all these animals live in southern countries, however, the Nordic man thinks of a hair covering in the sense of a mammalian attribute, and the paucity of human hair forms an intensely felt distinction between man and animal. With his actual paucity of hair man could not have inhabited the earth as far north as he did without clothing. He substituted the pelts of mammals, which made it possible. Scientific opinion regarding the cause for this absence of hairy covering in man is not yet established. The explanations accept a possible former aquatic life

of man's forebears, or, as the author has said, this scant or absent human hair covering is considered a consequence of domestication. A parallel could be drawn to the scarcity of hair and bristles of our domestic hog as compared with the abundance of bristles in the wild hog. Yet these explanations do not fully satisfy and do not entirely explain man's lack of hair. It can be understood only, if we think of the persistence of the baldness of nakedness observed in all anthropoid apes, persisting for the first weeks after birth in man. We must suppose that the development of a furry covering, which succeeds the nakedness at birth in the anthropoid apes, is hindered in the hominidae by certain hormones which have not yet been studied. An incomplete furry covering occurs in the male sex of human races who are relatively hairy, after the sexual organs have been developed, but it is very inconspicuous in the human races with scant hair.

Such physiologic considerations show that the influences active in hominidae in hindering rapid development of the terminal hair covering, as it is seen in anthropoid apes, must lie in the glands of internal secretion which are weakened by the development of the generative glands. The thymus gland, its relative size in anthropoid apes, would have to be studied. When the generative glands have developed the thymus gland atrophies and the terminal hairs sprout in man. That the thymus gland alone hinders the development of terminal hair in hominidae is very improbable, for probably a number of organs with internal secretion participate in the long-continued hair paucity of man. This discussion shows that man's scarcity of hair is one of the numerous characters which persists in man for a long time while it passes rapidly in other animals. The main zoölogic peculiarities of hominidae, aside from the persistence of infantile characters, and often associated with them are the signs of domestication. It was formerly not known that large anthropoid apes, gorilla, chimpanzee, and orang, are entirely naked for a few weeks after birth, like man, and like him, have a human cap of hair on their heads, in spite of their nakedness or rather scarcity of hair. The hair cap on the head of orang is not nearly as thick and complete as in the African anthropoids. The later paucity of man's hairy covering surprisingly resembles the paucity in newborn anthropoids, and, if the development of terminal hair covering is delayed from internal reasons the distinction between man and the present-day anthropoids

becomes conspicuous. Temporary nakedness is observed in none of the newborn hogs, not even in the wild groups, therefore the scarcity of bristles, persisting through life in the domestic hog, cannot be attributed to a retardation of the development of the definite hair covering. This describes the human nakedness as a distinct form, and partly explains it, for we must assume that the origin of hair covering in other naked animals has also been different from that described for hominidae. Numerous detailed studies on hair will be necessary to gain a satisfactory physiologic picture of the especial features of man's hair covering. The author often has pointed out that man is the only known mammal without blood-sac hairs, which all hair-bearing mammals are in the habit of developing first. In the morphology of man no temporary appearance of blood-sac hairs has been demonstrated. But, as orang also shows numerous degenerated and stunted blood-sac hairs in the beard region, man's lack of sinus hairs may be considered as not primary, but that he has lost them, while his ancestors had them. Of course this point calls, as do the formerly mentioned, for detailed morphologic and physiologic study. Nudity of the newborn with persistence of the scalp cap is found not only in anthropoid apes but, to a lesser extent, also in lower apes, but the young hapalidae, as the author found in his, born in captivity, are born with a dense fur covering, and do not pass through a stage of scarcity of hair when they change to their usual fur. In this respect they are like squirrels whom they resemble. Temporary, almost complete nakedness, was seen in newborn anthropoid apes so often that it is improbable that this condition represents an accidental finding. One may well assume that chimpanzee, orang, and gorilla regularly pass through a period of human nakedness after birth.

If the sexual urge is developed to an extent in some cases of male domestic animals, by excessive feeding, that hogs were covered by bucks, such results are entirely without significance for sheep breeding on account of the genetic situation which does not permit supervention of hereditary factors of hog in buck heredity, as hog and sheep cannot produce bastards. If one, however, crosses domestic sheep with various wild sheep new hereditary factors are introduced into sheep breeding, the heredity becomes split and thereby rejuvenated; new animal forms, which have never existed before, are extorted. The genetic situation of mankind is of a nature which

seems to exclude rejuvenation by mixing it with any living ape species, even if individual bastards might be produced.

As far as is known, all the various forms of hominidae are unrestrictedly fertile in crossing, so that the entire stock of living human material may be used for eugenic purposes to breed ideal races. In an opposite to this biologic conception is the far spread eugenic idea of a former ideal pure strain hereditary mixture in hominidae which has perished from intermixture, and that the purpose of perfection of the human race should reestablish this old ideal, eliminating the principle of mixture. In opposition to this view the author has stressed the conception that pure hereditary strains must be considered the end, but not the beginning, of developmental evolution, and that we must think of the animal forms of prehistory as of more split stock than the present well defined animal forms. Hominidae are the most "bastardized" of all animal forms living to-day, as no other was in a position to intermix constantly in migration over the entire globe, as did man. If numerous biologists have pointed to the persistence of infantile characteristics as the main human feature, this rejuvenation is the result of constant intermixture with closely related human forms. All domestic animals show signs of rejuvenation of their physical forms, because, through the will of man, a mixture of hereditary stock is accomplished which would not have occurred while they lived wild. Infantile characters result mainly in the skull and brain from such mixture, and the special form of the human brain has the outward juvenile appearance with the highest internal specialization.

It has been put thus: Man resembles a matured ape foetus. If this is the case ape fetuses must resemble man not yet matured, and that they do. The period of greatest resemblance, however, differs in the various ape types. Though the gorilla embryo does not resemble the human embryo, the height of resemblance occurs in the second and third years of life. The maximum resemblance, then, is not found very early in the development, as one used to believe, but, according to the rapidity of development of the individual body features, human resemblance increases with growth. Ape embryos do not only resemble human embryos, but the human embryos have so many characteristics which we now recognize as characteristics of present-day apes, that one does better by saying that they resemble

one another greatly. The idea that apes and all animals originated from man will probably soon be forsaken by those who hold this strange opinion. In animal species where, as in hominidae, constant rejuvenation takes place, the first part of their development does not only point back to the past, as stated by the biologic fundamental law, which reads: Evolution is the abbreviated recapitulation of the hereditary history. The first part of development in these cases points forward to the future of the species which is still capable of development. The second developmental period, in general, points forward, but in rejuvenated animal forms also points back to the past. For an example we mention the strong bony supraorbital arches, seen in many great men, such as Darwin and Nietzsche. They do by no means point to a future human race with strong supra-orbital arches but back to the past, when a large number of human forms had strongly protruding supraorbital arches. But the foreheads of present humans, and women with steep foreheads, are not only retrospect to the past, when human beings with steep foreheads lived, but also point to future man, when this feature will have attained permanency, while the anthropoid form will have died out. Because of the rejuvenation of mankind, by mixture, the infantile form is a pointer into the future, and not retrospect, and vice versa the terminal, or senile form, not anticipating but retrospect. To be exact, we must say, that the first developmental period of man is mainly retrospect, and in individual cases anticipatory, while the second part points, mainly, forward into the future, and backward only in individual characteristics. For backward or forward pointing of an animal species is decisive for ageing or rejuvenation. To develop pure lines is equivalent to ageing in an animal species, to become split is equal to rejuvenation and mutation of species. This explains the manifold vegetable and animal development of organisms in former times which was possible then, but not now. Rejuvenation by intermixture can produce limited mutation and new forms in man and domestic animals which for the overwhelming majority of organisms is much more difficult.

When the generative cells divide at maturity complicated forms of parthenogens are observed in the chromosomes, which become comprehensible when we consider the purpose of such complexity, that is prevention of excessive variability. Microscopic analysis of the

reduction of chromosomes shows that not half of the chromosomes are ejected, the other half remaining, but two most similar chromosomes attach themselves to each other and form a so-called dyade stage in mature segregation. After that these two similar chromosomes divide, and the total number of chromosomes in this cell is doubled. The dyades have changed to tetrades, that is, the chromosomes are united in bundles of four. Since man has forty-eight chromosomes the human cell, at least the female cell of the ovum, has ninety-six chromosomes in the tetrad stage, that is twice the number of the common cell. Not a decrease, but an increase of chromosomes is seen in this stage of parthenogenesis. Reduction to one-half is accomplished by two splits in the double number without interruption. In this process one of the four parts of the tetrad is allotted to each oval cell, and one each to every polar body. Thus two similar fractions can unite in any cell, as is the case in the mother cell. By this as yet unexplained process of initial, duplication and subsequent halving greater constancy of the fertilizable generative cell is possible than if the halving occurred right away. In pure strains the partners which have united to form dyades probably resemble each other so closely that all four cells resulting from their union have approximately the same hereditary factors. If, however, the cells were of split heredity the above-described mechanism of parthenogenesis causes two of each cell to have similar, and two to have different hereditary factors. It looks as though these complexities meant an adaptation for greatest possible preservation of the series in generative succession, while, without this explanation, the initial duplication and subsequent halving would seem unexplained.

We recognize an important factor in the necessary variation of all animal species in the reduction of number of the various chromosomes in parthenogenesis of the generative cells. If the animal-species man has forty-eight different chromosomes and twenty-four of them have to be thrown out (eliminated) before fertilization, purely according to the laws of chance it is not very likely that the same kind as the ejected chromosomes are reintroduced by the sperm, but the possibility cannot be denied entirely, for part of the chromosomes will probably return. At all events the difference of sex generative cells must constantly be reduced by maturity division, if new hereditary factors are not added by hybridization. At least seven genera-

tions would be required to change complete split heredity to pure hereditary lines in man, if panmixia had a maximum in mankind which would constantly delay pure strain formation.

We see that constant mutation of species is assured by lost mutants even is no selection by environment factors or change in any biologic surrounding factors seems apparent as a reason. Organisms which have developed pure strains show a surprising absence of change which may be preserved for entire epochs of this earth and last till the animal species becomes extinct. The form of the species has become entirely independent of the changes of environment, which they have to tolerate without adaptation, or the pure-strain species dies out if it cannot cope with the changed conditions.

The above-named cause for the variation of animal species which has not been discussed in literature so far, explains the resemblance of human races and anthropoid forms by the same loss mutation. Many scientists have noticed that the Negro and the gorilla, the orang and the Malayan, the European and the chimpanzee resemble one another, though we may not invoke descent as a reason. We need only assume that biologic factors cause a selection both in man and anthropoid for an explanation that dark-skinned men and dark-skinned anthropoid apes occur in the same neighborhood although no new blood relation has supervened. It is interesting to find that similarities include such of temperament, that is peculiarities of character. We find the slow, quiet manner, averse to noise of orang a trait of the eastern Asiatic human race; the noisy, playful temperament of chimpanzee enjoying loud sounds in the African human race. There is even a startling similarity in their dances. As has been mentioned above it can be explained by biologic selection of the same hereditary lost mutants in man and anthropoid of the same region, though commonly an attempt is made to attribute it erroneously to close blood relation. We must remember that man and anthropoid ape, and all ape species, with few exceptions, living in the Congo section have black skin, where it is not covered by hair. The lighter palms and soles of the negroes form an exception. One will hardly doubt that the climate must be invoked to explain the factor which favors the blackening. It is evident that heredity of acquired characteristics cannot be considered the cause.

Why bastards resemble the original types so closely will be seen



in considering the hereditary stock of hybrids and original forms. By reuniting the isolated hereditary factors by splitting, the former genetic situation is reëstablished. The picture of *Pithecanthropus* of Java and Peking shows that the reconstruction, though made exactly according to the remains, produced forms, which look as though one had tried to picture the intermediary bastard of the first generation of man and present-day anthropoid ape. This resemblance is explained by the above described splitting of hereditary stock of man and man ape from the same split hereditary ancestral forms, a segregation which would be rescinded by hybridization, by reunion. The author believes the naming of the remnants of forms found in the soil according to the present-day zoölogic species, erroneous, for those animals which are in the midst of morphologic change, while animals of the past, which have developed pure strains, may be designated with present zoölogic names. The preliminary forms of present species however, must always have been of split ancestry. Taunges ape, *Australopithecus africanus*, in South Africa, was not a chimpanzee, but a man ape, which united qualities, which today occur separately in anthropoid apes and man. His brain and peculiarities of teeth point to hominidae, the lower portion of the face to gorilla; the temporal angle to orang. Therefore we see many scientists vividly expressing the opinion that we should consider Taunges ape as a chimpanzee while others, with equal conviction, call him a gorilla, still others an orang-utang, and many point to the human resemblance of this prehistoric being. As morphology would have it, we find remains of animals in the soil which unite the characters of several species, as preliminary forms of these species. Therefore it is probable that preliminary forms resembling Taunges apes existed in the ascendancy of man, though *Australopithecus*, for that reason, could not be considered the original forefather of hominidae. *Australopithecus* and the Piltdown man have a cranial characteristic which orang alone, of all anthropoid apes, and man, have, that is the insignificance, or absence, of a brow ridge. This feature is evident among the black and yellow races, especially in the female, while the male of Europeans and aboriginal Australians, Ainos and Veddahs often have strong bony brow ridges which make their skulls resemble those of young chimpanzees, while skulls, without marked supra-orbital ridges in man greatly resemble those of young orangs.

The author supposes that black and yellow races, which in many respects represent the extreme contrasts occurring in mankind, originated from types with weakly developed hereditary factors for bony supraorbital ridges, that is preliminary types such as *Australopithecus* and *Pittdown man*. For our impression the teeth of the black and the yellow human beings, the *prodonia*, that is the slanting position of the teeth, is ape-like, while Europeans, as were the forebears of *hominidae*, are distinguished from the majority of ape species by their straight teeth; on the other hand they resemble them by their brow ridges. We may say that in Europeans the forehead, and in the black and yellow races, the teeth resemble those of most ape species. Two types of skulls must be distinguished in animals, balloon skulls and bone skulls. The balloon skull is the older only in this feature, for all fetuses of all animals have them. Now, this does not signify that formerly mammals lived with balloon skulls when mature, but we may expect the more pronounced bony skulls, the earlier the mammal forms we consider. Infantile forms may have occurred in single specimens in the later stages of life, where developmental arrest preserved foetal types. Only in recent times have types developed in man and his domestic animals which, from constant hybridization of similar but yet differentiated hereditary stock, preserved balloon skulls all through life. We find all stages in mankind, running from the complete balloon head of *Akka* dwarfs, or some of the Asiatics, to distinct bony skulls in Australian aborigines and some Europeans. We may assume that balloon shapes will become constantly more numerous among mankind in future, particularly if man should adopt eugenics and prefer those types, the central nervous system of which predominates over the rest of the germinal layers. Bony forms of skulls appear like anachronisms and ape-like types in spite of their frequent genius, because the majority of present apes do not have balloon skulls but bone heads. Vestiges of balloon heads are, however, apparently in some apes of the New World to-day, especially among *Cainchim* apes. By the way, it may be pointed out that the ratio of brain weight to body weight is equal or more favorable than that in man only in the New World apes. By no means does the intellect of the new world apes fall short of those of the old world, for they more readily use tools in captivity than do the anthropoids of the old world.

While all Neanderthal skulls are boneheads, Piltdown and Taunges apes are the first to show ancestors with preliminary formation indicating the balloon type, though the shape is not definitely developed. The Grimaldi race, which is considered the ancestor of Negroes, are characterized by marked cranial bulging and prodentia with prognathous jaws. Preliminary forms of the yellow race have not yet been discovered, but possibly they may be considered as having, like Piltdown man, steep foreheads, marked prodentia, or they may have resembled the preliminary forms of the yellow race in this respect. Every student of comparative anatomy will have noticed the resemblance which skulls of adult Negroes bear to those of orang children, and old Europeans to chimpanzee children. Even in early youth, in two-year-old chimpanzees, the supraorbital ridges are as much developed as they are in some full grown Europeans with strong brows. The forms of old males of Orang, Chimpanzee, and Gorilla when fully developed, as is well known, grow constantly more dissimilar to all forms of hominidae. In our domestic animals we have vestiges of such differences. If we compare the skull of dwarf dogs with those of young dogs we find the same resemblance to orang children as is seen in most human skulls, which, even in the adult resemble apes by the same weak bone formation. The larger dog races develop bone ridges on the formerly smooth infantile skull, which are less powerful than those of old male Gorilla and Orang, while Pekingese dogs, and man, have retained the younger balloon shape. We may say that the skull of a Pekingese has the same relation to the shepherd dog as the skull of modern man has to that of Gorilla. Zoölogists will note that closely related animals may have balloon or bone skulls in the same family, and that we need not overthrow the results of blood studies because of the differences presented by the skull form of man and present anthropoid apes. They demand classifying of man and present-day anthropoid apes in one zoölogical animal family, while an especial zoölogic order for hominidae seems less justifiable.

The abyss around the animal family, man, regarding tooth forms has been bridged. Not only does man share the dental formula with all Old World apes, but his teeth, with exception of the canines closely resemble those of female anthropoid apes, and none but expert investigators can diagnose them from tooth fragments. Not all hu-

man beings have the same dental formula, nor have all apes belonging to one species. Some gorilla specimens have four more molars than the average. They have not  $2/1/2/3$ , but  $2/1/2/4$ . Australian skulls can be found where four more molars existed than is the case in the average man.

Generally man, like other Old World apes, has but two sets of teeth deciduous and permanent, but a third set has been reported in some cases. Entire third sets have formed after the adult teeth were shed, which is not generally the case for man.

Only the gorilla teeth resemble those of American apes more than the rest of the Old World apes, and not the teeth of anthropoid apes, but in many respects those of certain female macacus most resemble those of man. The canines scarcely reaches above the row, and the occlusion is as close as that in man, which is generally not the case in anthropoid apes. The second lateral incisor of chimpanzee and other anthropoid apes does not have a straight border, like the central, it has a slanting border to give room to the protruding lower canine. Often a slant is found in the lateral incisor of hominidae, though the cause of giving room for the canine cannot be invoked. This may be considered a reminiscence of a former larger canine in human forebears, which is indicated by the large root as compared with the crown in to-day's man. There are many persons whose upper and lower canines protrude beyond the other teeth, although an even dental plate is characteristic of hominidae, not found in any of the other mammals. It is the most perfect chewing tool for grinding of vegetable seed, for which food man seems predestined. Only Pilt-down man has protruding canines, which makes him an exception yet to be explained. Generally speaking one may say that an even dental plate without protruding canines is characteristic for hominidae and it is an old characteristic human possession. The main resemblance of man and anthropoid apes as to denture, lies in the deciduous teeth, while in the permanent set distinct differences prevail both in canines and premolars. The maximum difference is found in the first bicuspid, while when chewed off, man's teeth are hard to distinguish from anthropoid apes'. Not in all respects did the molars of original man resemble those of present man, in spite of great similarity. Viewing resemblances and differences in the teeth

of hominidae and to-day's apes one sees that there are no unbridged chasms, for the differences are wiped out by individual variation.

Briefly summarizing what has been said, the most important difference between man and other animals is probably the predominant split-heredity of man in contradistinction to the preponderant pure heredity of organisms living wild, and not bred for domestication. Man's position in the animal world is characterized by the recognition that man and anthropoid apes have the same blood relation as have all other animals which are fertile in mating. The chasm appearing to-day between man and anthropoid apes would seem to be bridged if the remains found in the soil are of such a character that it would be difficult or impossible to decide whether to place them with the present anthropoid apes or with man himself. The missing link predicted by Darwin has been found in *Pithecanthropus* of Java and Peking. It is, however, improbable that there can be a single missing link, just as unlikely as there was a single forefather, and the remains of animal types will, in my opinion, be found at some future time which unite characteristics of hominidae and anthropoidae in a mixture differing from that found in *Pithecanthropus erectus*.

# Medical Questionnaires

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Collated by B. BICKEL, M.D.

Washington, D. C.

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## *How should one manage hoarseness?*

Normally the vocal cords have thin sharp borders. Swelling, thickening, ulcers, nodes, and disturbances of the nerve function may cause hoarseness. The borders fail to meet closely in any catarrh of the upper respiratory tract involving the mucous membrane of the larynx. The patient should not use his vocal cords, to avoid rubbing. Codein, diocid, acedicon, or opiates may be indicated; also papaverin, 0.04, or pantopon suppositories. For acute catarrhs, especially the infective type, sweating, induced by hot baths is recommended, or aspirin and salicyl. If expectoration is difficult give ipecacuanha, senega infusion or codyl sirup. Acute laryngitis may be favorably influenced by hot fomentations or hot-oil packs, and salt-sodium solutions for inhalation. Astringent swabs should not be employed for acute throat conditions. Subglottic laryngitis in children must be distinguished from laryngeal croup. The latter should be treated with serum, while the former calls for hot fomentations, sweating, and reduction of cough. Suppurative laryngitis associated with pain should be attacked with hot rinsing, artificial heliotherapy and incision deep into the tissue, and hot and cold compresses alternatingly. Chronic laryngitis may be caused by smoking. Give adrenalin, astringents, swab with 1-3 per cent. lapis solution, protargol solution, or mistol. Inhalations of oleum pin. pum, ol. therebinth., and pine spray are added. Inhalation of sodium bromide 2.0, cocain 0.2 with 200.0 distilled water, and a few drops of oleum menth. piper. Or menthol 2.0, 01. pin. purnil, ol. therebinth., ol. eucalypt, 10.0 equal parts in paraffin 200.0.—Lipiodol has been shown to cause untoward effects, so it is to be used with care where there are respiratory disturbances.—Generally normal lungs can expel accumulated secretions by motor action. Expectorants, such as ammonium chlorid start motor action in the bronchi. Potassium

iodide is a great help also. This has been shown by roentgenographs in animal experiments.—Recently laws in some European countries have greatly restricted the use of narcotics and many expectorants have been condemned on that account. Some of the vegetable decoctions used as house remedies have, there, gained ground. One of the tried remedies of this type is a primula and violet extract decoction. The action is probably due to a considerable saponin content.—More attention should be paid to mouth breathing. Considerable work is entailed in respiration. In order to supply the system with an adequate amount of air 13 cubic meters a day are necessary. During strenuous exercise an enormous amount of labor is expended in inspiration. Furthermore, the air must be warmed, during which process calories are lost, more so when the body renders the air filled with water vapor. The reduction of water into vapor also requires great calories expenditure. Bloeh has shown that the air is warmed mainly in the nasal cavity. The air passes through narrow passages in two columns, and the blood supply of the nasal mucous membrane is much more developed than that of the pharynx. The secretions are increased by contact with the cold air and warmth produced thereby. This secretion also protects from chilling and freezing. The vibrissae catch the lighter dust and bacteria; the heavier drop, the lighter are carried up into the horizontally placed nostrils. Air may suck them into the pharynx where they are deposited in children on the tonsils, in adults on the mucous membranes, where the direction of the air current changes. The inspiration through the narrow air passages is slow, and therefore the inspirations fewer and deeper. Mouth breathing allows nasal deposits to remain long, cause inflammation which extends to the accessory sinuses, and they are apt to produce purulent matter.

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*What are the differences between first infection and reinfection?*

Confusion has been produced by poor definitions of "infection." A pathogenic organism may lodge on the body without subsequent disease. A germ may touch the body and not be permanently lodged. Whether a germ can attach itself to the skin or other parts without causing reaction is not known. Reaction to a germ may, but does not necessarily, produce symptoms. The reactions consist of accumulation of cells or antibody formation. If infection is a mechanical process, the attachment without reaction—if there is such a thing—must likewise be mechanical. Deposit of the pathologic agent followed by reaction is a vital process, or, one may call it a biochemical process. There is no essential difference between the first infection and repeated, or reinfections. Both are in the first place mechanical, but the reactions are very different.—The second infection produces reactions more rapidly than the first, as v. Pirquet has proven for tuberculosis. Probably this is true of all infections, and yet the resulting diseases vary.—Cell affinity is the cause for the lodging of germs at certain points. The microbes may travel along the lymphatics or enter the blood stream, if there is an opening. They may lodge in the lymphatics or be carried to cells which are in a condition to harbor them. Germs may lodge at the place of entry in tuberculosis, syphilis, vaccinia. Wounds may be infected with them. Regional glands generally participate in the invasion.—Small hidden primary lesions are particularly common in malaria, mumps and infantile paralysis. Biologic tests have enabled us, only recently, to detect infections which cause no symptoms and cause no disease. There are many ways of infection, inhalation, ingestion, *etc.* As apparently healthy individuals harbor germs the moment of contact with the infection is hard to gauge; the quicker reaction of reinfection is better known. It has been shown that reinfection with syphilis may occur while the first infection still exists, and that renewed infection may result after complete cure from the first, with the same symptoms. Hamburger believes that in vaccination and tuberculosis the slight reaction is due to superinfection, not a reinfection. Reinfections with tuberculosis are many, and for most people of no consequence. Diphtheria infections must be common;



yet many persons never react to it, or react only under certain conditions, then the reactions may be very violent.

HAMBURGER, FRANZ: "Ueber Erstinfektion und Reinfektion." *Wien. klin. Wchnschr.*, vol. 44, pp. 533-550, 1931.

*Should massage be given after muscle exertion?*

Muscle pain after strenuous exertion starts within from twenty-four to thirty-six hours, and disappears within a few days. Quite commonly the same exercises as caused the pain are repeated to overcome it. However, sudden exertion of tense muscles may cause rupture. Stretching exercises are recommended by Finnish sportsmen, also hot-vapor baths, starting with 38° Celsius, rising to 41°, and to be continued not longer than twenty minutes. Some individuals are greatly benefited by massage after athletic overwork, others do not tolerate it. Deep hard handling must be avoided. Circumscribed hardening may persist for a time. If so, patient gentle rubbing around the area is indicated. Wachsmann recommends injection of  $\frac{1}{2}$ -2 cc. novocaine injections into these afflicted parts. Young asthenics are apt to lose their appetite and sleep. They should be advised to rest fifteen minutes before and after muscle work. A change in exercise should be recommended, rather than repetition of the former movements. The effect of massage after a period of exercise was studied upon 1,500 athletes. The metabolistic results indicate that massage, when intended for mild stimulation should be given after exercise or work. If it is to be a sedative, the people must rest at least one hour before they are treated with a full massage.

KOHBAUSCH, W.: "Behandlung der Ermüdung und Erschöpfung beim Sport." *Fortschr. d. Ther.*, vol. 7, pp. 281-284.

LAMPERT, HEINRICH: "Die Wirkung der Vollmassage nach Ruhe und nach Muskelanstrengung." *Klin. Wchnschr.*, vol. 10, pp. 832-834.

*Which cog in the therapeutic wheel seems most in evidence?*

From the popularity which articles on dietetics have at the moment, it would appear that the entire profession has adopted the policies of the old family physician and the housewife to reach the heart of the patient by way of the stomach. Means of influencing the entire body to elicit a salutary response of the system to outward influences and to disease are numerous. It has been recognized that,

in a manner, the daily diet constitutes a therapy to this end.—Simple reasoning shows that insufficient gastric secretion has the effect of insufficient chemical action upon the food. Insufficient digestion irritates the intestinal mucous membrane and, incompletely digested particles become putrefied (albumin) and ferment. Hydrochloric acid of the gastric juice has considerable antiseptic power. Cohnheim has shown that the only genuine protein digested by the proteolytic ferments of the pancreatic and gastric juices is caseine (except protamine and histone). It has been noted that susceptibility to infections, especially of the respiratory and intestinal tracts, is greater among animals on deficient diet. Changes from defective diet occur in the various body tissues and may be demonstrated by the microscope and chemical analysis. Patients with rickets have long been known to have an abnormal amount of calcium and inorganic phosphorus in their blood, and that diet may rectify this chemical fault. Centuries ago the Chinese and Phoenicians anticipated the deficiency existing in the thyroid gland in goitrous conditions, for they used the iodine-containing marine products to cure them. In 1820 Coindet had refined the method into therapeutic application of tincture of iodine to goiter. At present foodstuffs containing the small quantities of this dyad required by the body are diligently sought for an appropriate diet. Milk, vegetables, and fish supply the non-goitrous individual, and adequately they should be added to any iodine therapy.—Dietetics for diabetes have been most highly developed for several generations. Insulin treatment has more clearly demonstrated the actual necessities. But right now professional voices are heard with a doubtful note regarding these established metabolistic measures. Stolte and Hirsch-Kauffmann have let their diabetic patients eat carbohydrates. They found that less insulin was needed when a physiologic diet was permitted.—For patients with heart-disease Stein recommends restriction of liquids in cases without congestion. The fluids increase the amount of blood until they are eliminated. Where sclerosis is a feature, protein should be curtailed, especially that derived from animals, in order to avoid excessive blood formation, and because of the effect on the vascular walls. Food, rich in purine (brain, thymus, liver, kidney) are to be avoided. Spices and sharp sauces are harmful

where sclerosis is marked, also coffee, nicotine, and alcohol. Large meals are detrimental, and small frequent lunches to be preferred for the purpose of keeping the diaphragm in a low position.—Specialists are paying attention to their patients' diet. Obstetricians have recognized the value of dieting for many years to keep the fetus small in certain cases. Now they are acquiring the habit of giving women strict regulations. Novak, for instance, proposes 35–40 Kalories per kg. weight. War experiences in Europe demonstrated that meager diet reduced puerperal intoxication and eclampsia. He advises 100–120 Gms. albumin; 60 Gms. fat; much carbohydrate—the latter, he indicates, to avoid ketonuria and acidosis, if too little is given—350–450 Gms. Vitamins should be supplied in the form of green vegetables and fruit. Generally sufficient calcium is supplied, except where toxicosis, such as hyperemia, nephrosis, or eclampsia are feared. Too much salt increases the tendency for edema. Where vomiting is copious, intrarectal or intravenous feeding may have to be substituted. Novak and others believe that glycosuria of pregnancy requires no especial dieting. For habitual abortion iron and iodine have been useful. Fraenkel prescribes no variation from habitual feeding in the beginning of pregnancy, but after a few weeks some women require calcium and others acid. Calcium deficiency may lead to gestational caries or malacia of other parts. Recently vigantol, adrenalin, Roentgen-rays, and milk of castrated animals have been employed. Many obstetricians give cod-liver oil and potassium iodide to patients with habitual abortion. Aversion to certain food should be heeded, and the patients advised to have something on hand for sudden cravings. Careful moving is to be advised in the morning after a few mouthfuls of food have been taken, which may avoid vomiting. If the pelvis is narrow, reduction of carbohydrates and fluid is indicated. While labor is in progress no food is wanted or required, ordinarily. After the uterus has been emptied the gas-filled abdomen is sensitive to heavy food. Large quantities of vegetables at this time may cause distress. As soon as the parturient woman moves about she may eat whatever she likes, unless her diet has been obviously faulty.—McCarrison points out that surgical diseases may be produced by improper diet, and the surgeon understands that some cases, formerly his, can now be controlled by diet. Mellanby believes that vitamin A, derived from

milk, butter, eggs, and green vegetables, may safeguard our bodies from surgical infections. Improper feeding of rats produced damage to the lining of the entire digestive tract similar to that seen in human chronic colitis and stasis, also in the lining of the respiratory, urinary, and genital organs. The epithelial defense, he suggests, was broken down. It is necessary to uphold the epithelial system by adequate diet to avoid surgery.—Orr and Gilkes of the Privy Council for Medical Research have made interesting studies among two African tribes who have entirely diverse methods of nutrition. The Masai use much milk, meat, and raw blood, that is, much protein, fat, and calcium. The Kikuyu take much carbohydrate but little calcium. The full-grown Masai men are five inches taller and twenty-three pounds heavier than the Kikuyu, and their muscle strength is 50 per cent. greater. The Kikuyu have more bone deformities, dental caries, anemia, pulmonary diseases, and tropical ulcers; the Masai, more intestinal stasis, and rheumatic arthritis.—Levin and Silvers discuss the dietary pigments, referring to the yellow color of carotin, carrots, pumpkin, squash, and other vegetables; also of butter, fat, corpus luteum, etc. Rubner points to differences in food requirements, racial, familial, and individual. Constitution may be changed by diet. Old age needs different food because of changes in the teeth and other parts of the body. Habitual beer consumers choose other viands than those who prefer wine. The blood is changed every 70–90 days; the cells break down more gradually.

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### *What are indications for metal-salt therapy?*

Metal-salt therapy was primarily intended for infectious diseases. It was used to stimulate the body action, when given in small doses. This is the reverse of Ehrlich's chemotherapy which tries to attack the pathologic agent. Helms and Lunden tried manganum in tuberculosis, using 20-30 injections of 4 cubic centimeters of a 0.03 per cent. solution, twice a week, intravenously. Bacilli disappeared in from 58 per cent. of 162 patients, and good results were effected in 35 per cent. additional cases. After two years 15 per cent. of these patients were still at their work. Manganum and cadmium were used for dementia precox and other forms of insanity in Sweden, Holland, Czechoslovakia, Poland and Canada.—Calcium has been given for genital hemorrhages intravenously. V. Zalewski has given calcium *per os* for this condition, and for pruritus and exudative conditions, such as adnexitis, and bronchitis.—In our western plains, cattle chew bones found in the pastures when phosphate is lacking in their feed. Garden vegetables, especially tomatoes, lack manganese when grown in calcareous soil of southern Florida. The much-invoked vitamins which cannot be isolated chemically are not the only essentials for growth and welfare. Plants and animals consumed by man must contain them. Calcium, phosphorus, iron, iodine, manganese, copper, and zinc, seem indispensable, and like vitamins.—Farquharson and his co-workers found calcium elimina-

tion only slightly affected by large doses of alkali. The increased calcium excretion played a small part in balancing the excessive acid output, even though calcium of the urine was increased above the basal level. The quantitative increase of calcium excretion in response to ingestion of acid was greatly influenced by the basal level of the calcium excretion and by the amount of excess acid ingested.—Sodium chlorid is the only salt which it appears necessary to add to our diet. Other salts, important in our food, are present in sufficient amount both in animal and vegetable foodstuffs. All we eat contains about the same salts. Sugar has very little salt. Kestner says that calcium deficiency can arise only if milk is eliminated. Sufficient calcium is contained, he claims, for a nursing mother in half a liter cow's milk or a small quantity of cheese. Sodium chlorid is not contained in vegetable and animal cells, but in the blood and body fluids, in meat or other animal diet, also in milk and to a degree in vegetables. The reason for craving sodium chlorid is because it is eliminated by the perspiration. Furthermore the greater part of the daily amount of chlorid contained in the blood is poured into the stomach as hydrochloric acid, and more sodium than is contained in the blood is poured into the pancreas and intestinal juice as sodium hydrocarbonate. Kestner believes only the sweating man needs sodium chlorid. He believes that renal insufficiency is benefited by salt-free diet. This diet has been largely adopted in tuberculosis, eczema and other skin diseases. Kestner, however, states that the combination of blood salts cannot be influenced by dieting, nor the blood reaction changed by acid and alkali intake.—Herrmannsdorfer gave acid-producing diet, omitting salt, and a similar diet had been used in Sauerbruch's clinic. The theoretic foundation Sauerbruch admits as being weak. He believes that probably a vitamin effect enters into the success. Gerson introduced with this diet cod-liver oil, and phosphorus, which had been effective in tuberculosis for many decades. The early reports on such treatment were very satisfactory. Pisk could discover no improvement from it in sixty-nine patients with tuberculosis. Although good increase in weight was seen from it at the Brosby sanatorium, the impression was that this therapy did not replace others. Gerson himself reports quick reduction of night sweats from salt-free diet, and mucous secretion was reduced.

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